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Investigational Device Exemptions Manual

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U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FOREWORD

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA), develops and implements national programs to protect the public health in the fields of medical devices and radiological health. These programs are intended to assure the safety, effectiveness, and proper labeling of medical devices, to control unnecessary human exposure to potentially hazardous ionizing and non-ionizing radiation, and to assure the safe, efficacious use of such radiation.

The Center publishes the results of its work in scientific journals and in its own technical reports. These reports disseminate results of CDRH and contractor projects. They are sold by the Government Printing Office and/or the National Technical Information Service.

We welcome your comments and requests for further information.

D. Bruce Burlington, M.D,
Director
Center for Devices and
Radiological Health

PREFACE

To encourage the discovery and development of useful medical devices, the Medical Device Amendments of 1976 provided exemptions for investigational devices from premarket notification, premarket approval, and other controls of the Federal Food, Drug, and Cosmetic Act (the Act). An investigational device exemption (IDE) permits a device to be shipped in interstate commerce for clinical investigation to determine its medical safety and effectiveness. Although the IDE regulation exempts the device from certain requirements of the Act, it requires safeguards for humans who are subjects of investigations; maintenance of sound ethical standards; and procedures to assure development of reliable scientific data.

The term "medical device" describes a large and diverse set of products. Regulation of these products is a challenging and complicated process, not only because of the sheer volume and variety, but also because of their increasing importance in the delivery of patient health care. To aid manufacturers and clinicians in meeting these complex requirements, this publication deals with the procedures, rules, and safeguards that must be observed by those participating in the clinical testing of medical devices. Included in the publication are copies of applicable regulations together with an overview of the IDE regulation, policy and guidance discussions, and other explanatory matter. The basic material provided by this publication should acquaint you with the IDE process and should help you to focus on specific questions that you may wish to ask. Feel free to visit, write, or call the Division of Small Manufacturers Assistance (DSMA) either toll free at 800-638-2041, local at 301-443-6597, or fax 301-443-8818.

John Stigi
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Division of Small Manufacturers
Assistance

ABSTRACT

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This publication covers the regulatory requirements for investigational device exemptions, which are granted for purposes of conducting clinical studies. Although investigational devices are exempt from some regulatory controls, they must meet other requirements designed to safeguard human subjects of investigations, to maintain sound ethical standards, and to establish procedures that will assure development of sound scientific data.

The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

Although this guidance document does not create or confer any rights for or on any person and does not operate to bind FDA or the public, it does represent the agency s current thinking on investigational device exemptions.

Where this document reiterates a requirement imposed by statute or regulation, the force and effect as law of the requirement is not changed in any way by virtue of its inclusion in this document.

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Chapter 1, "Introduction," is an overview of the medical device regulations with general information pertaining to investigational device exemptions.

Products meeting the definition of a medical device under section 201(h) of the Federal Food, Drug and Cosmetic Act (FD&C Act) are regulated by the Food and Drug Administration (FDA). Medical devices are subject to general controls and other controls in the FD&C Act. General controls of the FD&C Act are the baseline requirements that apply to all medical device manufacturers. Unless specifically exempted, medical devices must be properly labeled and packaged, be cleared for marketing by the FDA, meet their labeling claims, and be manufactured under good manufacturing practices (GMP). FDA regulates devices to assure their safety and effectiveness. To fulfill provisions of the FD&C Act, FDA develops and promulgates rules to regulate devices intended for human use. These regulations are published in the *Federal Register*. Final regulations are codified annually in the Code of Federal Regulations (CFR). Most medical device regulations are described in Title 21 CFR Parts 800 to 1299.

WHAT IS A MEDICAL DEVICE

The definition of a medical device appears in section 201(h) of the FD&C Act. A device is "...an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component, part, or accessory, which is recognized in the official National Formulary, or the United States (U.S.) Pharmacopeia, or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes".

FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to

assure the safety and effectiveness of the device. The three classes and the requirements which apply to them are:

CLASS	REGULATORY CONTROLS
Class I	General Controls
Class II	General Controls and Special Controls
Class III	General Controls and Premarket Approval

GENERAL CONTROLS

As noted above, general controls are the baseline requirements of the FD&C Act that apply to all medical devices. Unless specifically exempted by regulation, general controls contain **requirements** for device manufacturers or other designated persons to:

- comply with the registration and listing regulations in 21 CFR Part 807;
- comply with the labeling regulation in 21 CFR Part 801, 809 or 812;
- comply with the reporting regulations in 21 CFR Part 803 and 804;
- submit a premarket notification [510(k)] (21 CFR Part 807) to FDA; and
- design and produce devices under good manufacturing practices (GMP) (21 CFR Part 820).

The controls in the above list other than reporting regulations are briefly described in this chapter.

Registration and Listing

Section 510 of the FD&C Act requires that U.S. device manufacturers and distributors register their establishments with FDA on form FDA-2891. All manufacturers are required to list the generic type of devices they have in U.S. commerce with FDA on form FDA-2892. Establishment registration and medical device listing should be submitted prior to commercial distribution.

Labeling

All medical devices in U.S. commerce must be properly labeled. Device labeling requirements of the FD&C Act are found in the following parts of Title 21:

General Device Labeling	21 CFR Part 801
In Vitro Diagnostic Products	21 CFR Part 809
Investigational Device Exemptions	21 CFR Part 812
Good Manufacturing Practices	21 CFR Part 820
General Electronic Products	21 CFR Part 1010

Basic labeling requirements and recommended labeling for medical devices can be found in the booklet, *Labeling; Regulatory Requirements for Medical Devices*, available from the Division of Small Manufacturers Assistance (DSMA).

Good Manufacturing Practices

As required by section 520(f) of the FD&C Act, the GMP regulation covers the methods used for, and the facilities and controls used for, the design, manufacture, labeling, packaging, storage, and installation of devices. The GMP regulation is codified in 21 CFR Part 820. Some class I devices, such as an manual surgical instruments for general use, 21 CFR Section 878.4800, are exempt by regulation from **most** of the GMP requirements.

The GMP regulation contains general quality assurance (QA) or quality system requirements in areas of concern to all manufacturers of finished devices. Among other requirements, it covers organization and personnel; design practices and procedures (proposed); buildings and environmental control; design of labeling and packaging; controls for components, processes, packaging and labeling; finished device evaluation; distribution and installation; device and manufacturing records; complaint processing; and QA system audits.

SPECIAL CONTROLS

In addition to general controls, class II and III devices are subject to further requirements such as special controls and premarket approval.

Class II devices are defined in section 513(a)(1)(B) of the FD&C Act to include any device for which reasonable assurance of safety and effectiveness can be obtained by applying ‘‘special controls.’’ Only general controls will apply to class II devices until special controls are established by regulation(s). Special controls may include special labeling requirements, mandatory performance standards, patient registries and postmarket surveillance.

PREMARKET NOTIFICATION

A premarket notification [510(k)] is a marketing application submitted to FDA to demonstrate that a medical device is as safe and as effective or substantially equivalent to a legally marketed device that was or is currently on the U.S. market and that does not require premarket approval. The premarket notification requirements are found in 21 CFR Part 807, Subpart E.

Most devices are cleared for commercial distribution in the U.S. by the premarket notification [510(k)] process. Most class I devices are exempt from the 510(k) requirement by regulation. However, they are not exempt from other general controls, such as establishment registration and device listing. Before marketing a medical device which is not exempt from the marketing clearance process, the manufacturer must submit a premarket notification [510(k)] or a premarket approval (PMA) application to FDA. The manufacturer cannot market the device unless the firm receives a marketing clearance letter from FDA as stated in section 513(i)(1)(A) or section 515(d)(1)(A)(I) of the FD&C Act. Detailed guidance on the 510(k) requirements can be

found in the manual, *Premarket Notification 510(k): Regulatory Requirements for Medical Devices*, available from DSMA.

PREMARKET APPROVAL

Premarket approval (PMA) is the FDA process to evaluate the safety and effectiveness of class III devices. Class III is the most stringent regulatory category for medical devices. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of class III devices.

Under section 515 of the FD&C Act, devices placed into class III by FDA are subject to premarket approval requirements. The PMA requirements are found in 21 CFR Part 814. Not all class III devices require an approved PMA to be marketed at this time. Class III devices that are substantially equivalent to devices legally marketed before May 28, 1976, and do not currently require premarket approval may be marketed through the premarket notification [510(k)] process until FDA publishes a regulation requiring the submission of a PMA for those class III devices.

Premarket approval is the process of scientific and regulatory review to ensure the safety and effectiveness of class III devices. An approved premarket approval application (PMA) is, in effect, a private license granted to the applicant for marketing a particular medical device. A class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the FD&C Act and cannot be marketed.

Detailed guidance on PMA requirements can be found in the *Premarket Approval Manual*, available from DSMA.

INVESTIGATIONAL DEVICE EXEMPTIONS

To allow manufacturers of devices intended solely for investigational use to ship devices for use on human subjects (clinical evaluation), the FD&C Act authorizes FDA to exempt these devices from certain requirements of the Act that would apply to devices in commercial distribution. Clinical evaluation of devices not cleared for marketing, unless exempt, requires an approved investigational device exemption (IDE) either by an institutional review board (IRB) or an IRB and FDA, informed consent for all patients, adequate monitoring and necessary records and reports. These requirements can be found in 21 CFR Parts 50, 56, and 812.

An approved IDE application permits a device, that would otherwise be subject to marketing clearance, to be shipped lawfully for the purpose of conducting a clinical study. This allows a researcher to use a device in studies undertaken to develop safety and effectiveness data for that device when such studies involve human subjects. The FDA is authorized to grant an IDE by section 520(g) of the FD&C Act.

In addition to allowing the shipment of a device for human clinical studies, an approved IDE application also exempts a device from certain sections of the FD&C Act; for example, misbranding under section 502; registration, listing and premarket notification under section 510; performance standards under section 514; premarket approval under section 515; banned devices under section 516; records and reports under section 519; restricted device requirements under section 520(e); good manufacturing practice requirements under section 520(f) unless the sponsor states an intention to comply with these requirements under sections 812.20(b)(3) or 812.140(b)(4)(v); and color additive requirements under section 721.

The three primary regulations regarding clinical studies included in the Code of Federal Regulations, Title 21 (21 CFR), are:

- Part 812 which provides the procedures for the conduct of clinical studies with medical devices (see Appendix A);

- Part 50 which provides the requirements and general elements of informed consent (see Appendix B); and

- Part 56 which provides the procedures and responsibilities for institutional review boards (IRBs) (see Appendix C).

All clinical investigations of devices must have an approved IDE or be exempt from the IDE regulation. Exempted investigations are described in section 812.2(c) of the IDE regulation which is provided in Appendix A of this manual.

Investigations which are not exempt from the IDE regulation are subject to differing levels of regulatory control depending on the level of risk. The IDE regulation distinguishes between significant and nonsignificant risk device studies and the procedures for obtaining an IDE differ accordingly. The determination of whether a device study presents a significant risk is initially made by the sponsor of the device. A proposed study is then submitted to an IRB for review. If the IRB agrees with the sponsor that the device study presents a nonsignificant risk, no IDE submission to FDA is necessary. A sponsor of a significant risk device study must obtain both IRB and FDA approval before beginning the study. Chapter 4 presents additional guidance on the different requirements for significant and nonsignificant risk device studies distinguishing between these types of studies in the document "Guidance on Significant and Nonsignificant Risk Device Studies".

Sponsors wishing to conduct investigations of banned devices should not begin an investigation before obtaining written FDA approval. All investigations of banned devices are considered to present a significant risk.

In order to conduct a significant risk device study, a sponsor must:

- submit the investigational plan and report of prior investigations (see sections 812.25 and 812.27) to the IRB for review and approval;

- submit a complete IDE application (see section 812.20 and chapter 3 of this manual) to FDA for review and obtain FDA approval of the IDE; and

- select qualified investigators, provide them with all necessary information on the investigational plan and report of prior investigations, and obtain signed agreements from them.

Upon receipt of an IDE application, sponsors are notified in writing of the date that FDA received the original application and the IDE number assigned. Receipt of supplements and amendments are not acknowledged. Within 30 days from the date of receipt, FDA will approve, approve with conditions, or disapprove an IDE application. In cases of disapproval, a sponsor has the opportunity to respond to the deficiencies and/or request a regulatory hearing under 21 CFR Part 16.

Once an IDE application is approved, the following requirements must be met in order to conduct the investigation in compliance with the IDE regulation:

- Labeling - The device must be labeled in accordance with the labeling provisions of the IDE regulation (see section 812.5) and must bear the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."

- Distribution - Investigational devices can only be distributed to qualified investigators;

- Informed Consent - Each subject must be provided with and sign an informed consent form before being enrolled in the study (see Appendix B, “Protection of Human Subjects” regulation which includes the requirements for obtaining informed consent);

- Monitoring - All investigations must be properly monitored to protect the human subjects and assure compliance with approved protocols (see "Guideline for the Monitoring of Clinical Investigations" in chapter 4 of this manual);

- Prohibitions - Commercialization, promotion, and misrepresentation of an investigational device and prolongation of the study are prohibited (see section 812.7); and

- Records and Reports - Sponsors and investigators are required to maintain specified records and make reports to investigators, IRBs, and FDA (see sections 812.140 and 812.150).

Obtaining approval for an IDE application is not a simple process. FDA realizes that filing an IDE application may be the sponsor's first contact with the agency. This manual has been designed to assist those sponsors. Chapter 2 is an overview of the IDE regulation and subsequent chapters present information on specific topics in the IDE program.

In addition to using this manual, sponsors are encouraged to contact FDA to obtain further

guidance prior to the submission of an IDE application. This will be especially beneficial to new sponsors who have not previously had contact with the agency and for sponsors proposing to study new technologies or new uses for existing technologies. Early interaction with the agency should help to increase the sponsor's understanding of FDA requirements, regulations, and guidance documents, and will allow FDA personnel to familiarize themselves with the new technologies. Increased interaction between FDA and sponsors should help to speed the regulatory process and minimize delays in the development of useful devices intended for human use.

Chapter 4 provides a list of device specific guidance documents that have been prepared by the Office of Device Evaluation which are available from the Division of Small Manufacturers Assistance, telephone (301) 443-6597 or (800) 638-2041; FAX (301) 443-8818; Facts-on-Demand (301) 827-0111 or (800) 899-0381. Sponsors are especially encouraged to contact the review divisions within the Office of Device Evaluation to discuss device-specific requirements. The IDE staff may be contacted for general questions relating to the IDE regulations on (301) 594-1190.

In addition to telephone contacts and meetings, sponsors may submit preliminary information as a "pre-IDE" submission. A pre-IDE submission may be used to obtain preliminary FDA input on preclinical testing, proposed protocol, etc. A pre-IDE submission may also be used to obtain FDA guidance on protocols for foreign studies that are intended to support future applications for marketing clearance in the U.S.

A pre-IDE submission must be clearly identified as such, submitted in triplicate, and should be addressed to:

Center for Devices and Radiological Health
Food and Drug Administration
IDE Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, MD 20850

New Regulations

November 1, 1995, was the effective date for a new rule which will permit reimbursement of certain investigational medical devices. The devices that will be considered for possible coverage are those investigational devices for which the FDA has determined that the device type can be safe and effective. FDA will identify those investigational devices that are of a type for which the underlying questions of safety and effectiveness have been resolved. These devices may be covered if all other applicable Medicare coverage requirements are met. It is hoped that this new regulation will provide Medicare beneficiaries with greater access to advances in medical technology and encourage clinical researchers to conduct high quality studies of newer technologies.

Future Regulations

Although not in place at the time of publication of this manual, a number of regulations are currently being worked on which will affect investigational devices. These are outlined as follows:

Revocation of Part 813. FDA has proposed to remove the regulations on investigational exemptions for intraocular lenses (IOLs) (21 CFR Part 813). FDA believes that it is no longer necessary to maintain particularized regulations on IOL investigations because approved IOLs are now widely available and investigations of IOLs can be conducted under the investigational device regulations applicable to medical devices generally.

Disqualification of clinical investigators. Procedures for disqualification of clinical investigators currently exist under the investigational new drug application regulations (21 CFR Part 312). In order to further implement the agency's plan for consistent bioresearch monitoring regulations for all products regulated by FDA and to improve the remedies available to deal with clinical investigator misconduct, FDA is amending the IDE regulations (21 CFR Part 812) to include similar provisions.

Financial disclosure. There is growing recognition of the potential for certain financial arrangements between clinical investigators and product sponsors, as well as the personal financial interests of clinical investigators, to introduce bias into a clinical trial. To address these concerns, FDA has proposed regulations that would require sponsors, at the time any marketing application containing clinical data is submitted to the agency, to disclose certain financial interests or arrangements, or to certify as to their absence.

Humanitarian device exemption. The Safe Medical Devices Act (SMDA) of 1990 provided for a humanitarian device exemption to encourage the discovery and use of devices that benefit fewer than 4,000 individuals in the U.S. This provision would allow FDA to grant an exemption from the effectiveness requirements of sections 514 (Special Controls) and 515 (Premarket Approval) of the FD&C Act after finding that:

- the device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the U.S.;

- the device is not available otherwise, and there is no comparable device available to treat or diagnose the disease or condition; and

- the device will not expose patients to unreasonable or significant risk, and the benefits to health from the use outweigh the risks.

Devices granted an exemption may only be used at facilities that have an established institutional review committee, and the humanitarian use must be approved by the committee before studies begin. An exemption would be granted for a period of 18 months and may be

granted in the 5-year period from the date regulations take effect. The 18-month exemption may be extended.

Revision of the Current Good Manufacturing Practices (CGMPs) Regulation. The SMDA also provided FDA explicit authority to add preproduction design controls to the CGMP regulation. The revised CGMP regulation will be referred to as the Quality Systems (QS) regulation. This change was based on findings that a significant proportion of device recalls were attributed to the faulty design of the product. Additionally, SMDA also encourages FDA to work with foreign countries toward mutual recognition of CGMP requirements.

Design controls. FDA believes that it is reasonable to expect manufacturers who design devices to develop the designs in conformance with design control requirements and that adhering to such requirements is necessary to adequately protect the public from potentially harmful devices. The design control requirements are basic controls needed to ensure that the device being designed will perform as intended when produced for commercial distribution. Clinical evaluation is an important aspect of the design verification and validation process during the design and development of the device. Since some of the device design occurs during the IDE stage, it is logical that manufacturers who intend to commercially produce the device follow design control procedures. If a manufacturer were to wait until the IDE studies were complete, it would be too late to take advantage of the design control process, and the manufacturer would not be able to fulfill the requirements of the quality system regulation for that device.

The FDA does not expect any new information in IDE applications as a result of this amendment. Nor will FDA inspect design controls during bioresearch monitoring inspections. The FDA will make a conforming amendment to the IDE regulation to make clear that design controls must be followed when design functions are undertaken by manufacturers, including design activity which occurs under an approved IDE. The FDA will evaluate the adequacy of manufacturers' compliance with design control requirements in routine quality systems inspections, including preapproval inspections for PMAs.

Human factors issues. The QS regulation will also require manufacturers to address human factors issues during device design and development. “Human factors” is a discipline that encompasses the various methods used to improve human/equipment compatibility, including the user interface, user instructions, and training programs.

Health professionals vary greatly in physical, sensory, and cognitive abilities. The increasing lay user population extends this variability even further. At the same time, medical devices are used in many environments and often in situations where conditions are adverse. These issues affect the nature and complexity of the user interface. The interaction of the user's capabilities, the operating environment, and device user interface will determine the extent to which a device is used safely and effectively.

The various methods contained within the discipline of human factors engineering address these issues. Manufacturers will be required to demonstrate that the appropriate human factors

methods have been utilized to optimize the device user interface given the abilities of the intended user and the
demands of the use environment. There are a variety of methods that may be used and some examples are: 1) review of the literature on device use, 2) review of incident reports and recall data, 3) function analysis, 4) task analysis, 5) hazard analysis, and 6) usability tests designed to obtain user experience data. The CGMP regulation does not specify which human factors methods are to be used, but the manufacturer is required to demonstrate that appropriate human factors methods have been used in the device design and development.

At this time, no changes to the IDE application or review process are anticipated. The above information is only being provided so that manufacturers are aware of the changes in the CGMP requirements as early in the device development process as possible.

More information on human factors testing can be obtained from the booklet entitled, "Do It by Design," available from the Division of Small Manufacturers Assistance (DSMA).

HOW TO GET MEDICAL DEVICE INFORMATION FROM FDA

Manufacturers and others who are interested in medical device regulatory requirements can obtain the latest information from DSMA. DSMA was mandated by the 1976 medical device legislation to help manufacturers comply with FDA requirements for medical devices by providing technical assistance and regulatory guidance.

Manufacturers can call 800-638-2041, 301-443-6597, send Email to DSMO@CDRH.FDA.GOV or FAX 301-443-8818 to get technical assistance or regulatory guidance, or to obtain FDA publications including FDA manuals and premarket review guidance documents. DSMA staff is available to answer questions by phone from 9 am to 5 pm Eastern Standard Time, by fax or by letter. DSMA offers two or three-day workshops on current regulatory issues such as premarketing submissions and CGMP held at various locations throughout the U.S. DSMA publishes various documents including 510(k), IDE, PMA, and GMP manuals. Many manuals are available at the workshops, from the Government Printing Office (202-783-3238) or the National Technical Information Services (NTIS) (703-487-4650).

CDRH Facts-On-Demand allows access to obtain CDRH information, 24 hours a day, 7 days a week by calling 800-899-0381 or 301-827-0111 from a touch-tone phone. Using the telephone keypad and following the voice prompts, the caller can access the CDRH Facts-On-Demand and request a DSAM Facts index or enter the three or four digit Shelf number for the document(s) they want. The DSMA Facts index & documents that are less than 30 pages are put in queue to be automatically faxed to the number provided by the requester. Documents that are greater than 29 pages are faxed after normal business hours.

2 OVERVIEW OF THE IDE REGULATION

GENERAL PROVISIONS
APPLICATION AND ADMINISTRATIVE ACTION
RESPONSIBILITIES OF SPONSORS
IRB REVIEW AND APPROVAL
RESPONSIBILITIES OF INVESTIGATORS
RECORDS AND REPORTS

This chapter summarizes the IDE regulation as codified in Title 21, Part 812 of the Code of Federal Regulations (21 CFR Part 812). Some of the material has been reprinted verbatim from the CFR while others have been modified for clarity. Section numbers of the regulation are identified in parentheses for reference to the regulation which is reprinted in Appendix A of this manual.

SUBPART A -- GENERAL PROVISIONS

Scope (812.1)

The purpose of the investigational device exemptions (IDE) regulation is to encourage the discovery and development of useful devices intended for human use while protecting the public health. It provides the procedures for the conduct of clinical investigations of devices. An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with special controls or having marketing clearance from FDA. An IDE application approved for a significant risk study under section 812.30 or considered approved for a nonsignificant risk device study under section 812.2(b) exempts a device from other provisions of the Food, Drug, and Cosmetic Act (FD&C Act) including misbranding (section 502); registration, listing, and premarket notification (section 510); performance standards (section 514); premarket approval (section 515); banned devices (section 516); records and reports (section 519); restricted device requirements [section 520(e)]; good manufacturing practice requirements [section 520(f)] and color additive requirements (section 721).

Applicability (812.2)

General. The IDE regulation applies to all clinical investigations of devices to determine safety and effectiveness.

Abbreviated requirements (nonsignificant risk device study). A nonsignificant risk device study is considered to have an approved IDE application, unless FDA has notified the sponsor that an application is required, provided that the device is not a banned device and the sponsor:

- labels the device in accordance with the IDE regulation (see section 812.5);

- obtains and maintains Investigational Review Board (IRB) approval throughout the investigation as a nonsignificant risk device study;

- makes certain that investigators obtain and document from each subject informed consent according to Part 50, unless documentation is waived by an IRB in accordance with section 56.109(c);

- complies with IDE requirements for monitoring the investigation (see section 812.46);

- maintains records and makes reports as required by the IDE regulation;

- makes sure that participating investigators maintain records and make reports as required; and

- complies with prohibitions on promotion, test marketing, commercialization of investigational devices, and unduly prolonging an investigation (see section 812.7).

Exempted investigations. The following device investigations are exempt from the requirements of the IDE regulation:

- a device, other than a transitional device (see section 812.3 for definition), in commercial distribution before May 28, 1976, when used or investigated in accordance with the labeling in effect at that time (preamendment device);

- a device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution before May 28, 1976, and that is used or investigated in accordance with the labeling that FDA reviewed to make the substantially equivalent determination (postamendment device);

- a diagnostic device if it complies with the requirements in section 809.10(c) and if the testing:

  - ....is noninvasive;

  - ....does not require an invasive sampling procedure that presents significant risk;

  - ....does not by design or intention introduce energy into a subject; and

  - ....is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure;

- a device undergoing consumer preference testing, testing of a modification, or testing of a combination of devices in commercial distribution, if the testing is **not** to determine safety or effectiveness and does not put subjects at risk;

- a device intended solely for veterinary use;

- a device shipped solely for research with laboratory animals and labeled in accordance with section 812.5(c);

- a custom device as defined in section 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution; and

- an intraocular lens (IOL) which is subject to an approved IDE under Part 813 or an approved PMA. All clinical investigations of IOLs are subject to FDA approval of an IDE application and must be conducted in accordance with Part 813.

Depending upon the nature of the investigation, those studies which are exempt from the requirements of the IDE regulation may or may not be exempt from the requirements for IRB review and approval under Part 56 and the requirements for obtaining informed consent under Part 50. For guidance regarding the applicability of these regulations with respect to investigations being conducted under the provisions of 812.2(c), contact the reviewing IRB and/or the IDE Staff at (301) 594-1190.

Limit on certain exemptions. For a class II or a class III device discussed above as a "preamendment" or "postamendment" device, the IDE regulation applies at the time that a pre-market approval application is called for by FDA for an unapproved class III device or when a performance standard for a class II device becomes effective.

Definitions (812.3)

Some of the pertinent definitions used in the IDE regulation are as follows.

- **Custom device** is a device that: (1) necessarily deviates from devices generally available ... in order to comply with the order of an individual physician or dentist; (2) is not generally available or used by other physicians or dentists; (3) is not generally available in finished form for purchase or dispensing; (4) is not offered for commercial distribution; and (5) is intended for use by an individual patient named in the order or to meet the special needs of the physician or dentist.

- **Implant** is a device that is placed into a surgically or naturally formed cavity of the human body if the device is intended to remain there for a period of 30 days or more. In order to protect public health, FDA may determine that devices placed in subjects for shorter periods are also implants.

- **Institutional Review Board (IRB)** is a board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of human subjects. The IRB should be established, operated, and functioning in conformance with Part 56. The term has the same meaning as "institutional review committee" in section 520(g) of the FD&C Act.

- **Investigation** is a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

- **Investigational device** is a device, including a transitional device, that is the object of an investigation.

- **Investigator** is an individual who actually conducts an investigation, i.e., under whose immediate direction the investigational device is administered, dispensed to, or used on a subject. In the event of an investigation being conducted by a team of individuals, "investigator" refers to the responsible leader of that team.

- **Monitor.** When used as a noun, is an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor, or a consultant to the sponsor, or an employee of or consultant to a contract research organization. When used as a verb "monitor" means to oversee an investigation.

- **Significant risk device** is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to a subject.

- **Sponsor** is a person or other entity that initiates but does not actually conduct the investigation. An entity other than an individual (e.g., a corporation or an agency) which uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor, not a sponsor-investigator, and the employees are considered to be investigators. The sponsor of an IDE must be located in the United States (see section 812.18).

- **Sponsor-investigator** is an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed, or used. The term does not, for example, include a corporation or agency. The obligations of a sponsor-investigator include those of an investigator and those of a sponsor.

- **Subject** is a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

- **Transitional device** is a device subject to section 520(l) of the FD&C Act and which FDA previously regulated as a new drug or an antibiotic drug before May 28, 1976.

- **Unanticipated adverse device effect** is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Labeling of investigational devices (812.5)

Contents. An investigational device or its immediate package must bear a label with the following information:

- the name and place of business of the manufacturer, packer, or distributor;
- the quantity of contents if appropriate; and
- the statement, "CAUTION -- Investigational device. Limited by Federal (or United States) law to investigational use."

The label must describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

Prohibitions. The labeling of an investigational device must not contain any false or misleading statements nor imply that the device is safe or effective for the purposes being investigated.

Animal research. The label of an investigational device shipped for research on laboratory animals must contain the following statement: "CAUTION -- Device for investigational use in laboratory animals or other tests that do not involve human subjects."

Prohibition of promotion and other practices (812.7)

A sponsor or investigator, or a person acting on their behalf, must not:

- promote or test market an investigational device until the device is approved for commercial distribution;

- commercialize an investigational device by charging the subjects or investigators a higher price than is necessary to recover the costs of manufacturing, research, development, and handling;

- unduly prolong an investigation; or

- represent that an investigational device is safe and effective.

Waivers (812.10)

A sponsor may request FDA to waive any requirement of the IDE regulation. A waiver request with supporting documentation may be submitted as part of an application or separately. FDA may, by letter (see Chapter 4, "IDE Guidance and Policies"), grant a waiver of any requirement that is not required by the FD&C Act and that is unnecessary to protect the human subjects.

Import and export (812.18)

A person who imports or offers to import an investigational device shall be considered an agent for the foreign exporter and shall either act as the sponsor of the clinical investigation or ensure that another person acts as the agent and the sponsor of the investigation. This means that the sponsor of an IDE must be located in the United States. Export of an investigational device is subject to section 801(e) of the FD&C Act, i.e., it is necessary to obtain FDA approval prior to export. This is due to the fact that FDA does not have jurisdiction over foreign studies conducted with medical devices and an IDE is not necessary for a study conducted entirely at foreign sites.

Recent Changes

On April 25, 1996, Congress amended Chapter VIII of the Food, Drug & Cosmetic Act which covers the import and export of FDA regulated products. Some major changes include:

Imports for Export - U.S. firms will be able to freely import component parts or accessories to medical devices without prior FDA clearance if they are intended for incorporation in medical devices that will be exported from the U.S.

Export of Certain Devices - Sections 801(e)(1) and (e)(2) are no longer the sole sections of Chapter VIII which apply to medical devices. Section 802 which previously applied only to drugs has been extended to address medical devices.

The export of medical devices was a two tiered system:

- they could be exported without prior FDA permission if they met the requirements of 801(e)(1) and were not excluded under section 801(e)(2).

- unapproved devices excluded under section 801(e)(2), i.e., devices which require and do not have a PMA, devices which do not meet section 514 performance standards, devices which are not exempt under an IDE, or banned devices, can be exported only after obtaining written permission from FDA.

Changes in Chapter VIII now add a third tier:

- unapproved devices excluded under section 801(e)(2) can also be exported, wihtout prior FDA permission, if they meet criteria specified in section 802. Devices exported under section 802 must comply with the laws of the country to which exported and have valid marketing authorization by the appropriate authority, specifically:

  - to Australia, Canada, Israel, Japan, New Zealand, Switzerland, or South Africa, or
  - to the European Union or a country in the European Economic Area **if** the device is authorized for general marketing in the European Economic Area, or
  - to additional countries to be designated by FDA which meet certain statutory or regulatory requirements and controls.

Persons can now request that the FDA certify in writing within 20 days of receipt that the device being exported meets the requirements of sections 801(e)(1) or 802. In addition, the FDA must provide written certification within 20 days indicating that it meets the applicable requirements of the FD&C Act.

At the time of this writing the amended copy of the FD&C Act has not been received in its final form and policy guidelines have not been established. Future revisions will reflect interpretations of the import and export changes to the FD&C Act.

Address for IDE correspondence (812.19)

All correspondence relating to an IDE should be addressed to:

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, MD 20850

The outside wrapper of each submission should identify the contents, for example, "IDE Application," "Supplemental IDE," "Waiver," etc.

SUBPART B -- APPLICATION AND ADMINISTRATIVE ACTION

Application (812.20)

There is no preprinted form for an IDE application, but the following information must be included in an IDE application for a significant risk device investigation. A sponsor cannot begin a significant risk device investigation until FDA and IRB approval are granted. **Three** copies of a

signed IDE application are required and the application shall include:

- name and address of sponsor;
- a complete report of prior investigations (see section 812.27);
- an accurate summary or a complete investigational plan (see section 812.25);
- a description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and installation of the device;
- an example of the agreements to be signed by the investigators (see section 812.43 for requirements for agreement) and a list of the names and addresses of all investigators;
- certification that all investigators have signed the agreement, that the list of investigators includes all investigators participating in the study, and that new investigators will sign the agreement before being added to the study;
- a list of the names, addresses, and chairpersons of all IRBs that have or will be asked to review the investigation and a certification of IRB action concerning the investigation (when available);
- the name and address of any institution (other than those above) where a part of the investigation may be conducted;
- the amount, if any, charged for the device and an explanation of why sale does not constitute commercialization;
- a claim for categorical exclusion (as provided for in 21 CFR 25.24, for example, by stating "Devices shipped under the investigational device exemption are intended to be used for clinical studies in which waste will be controlled or the amount of waste expected to enter the environment may reasonably be expected to be nontoxic") or provide an environmental assessment (as provided for in 21 CFR 25.31);
- copies of all labeling for the device;
- copies of all informed consent forms and all related information materials to be provided to subjects; and
- any other relevant information that FDA requests for review of the IDE application.

FDA may request additional information about an investigation. The sponsor may provide the requested information or the sponsor may treat such a request as a disapproval of the application and request a hearing under Part 16.

Information previously submitted to FDA in accordance with Part 812 may be incorporated by reference.

Investigational plan (812.25)

The investigational plan shall include the following items in the following order:

- purpose (the name and intended use of the device and the objectives and duration of the investigation);
- protocol (a written protocol describing the methodology to be used and an analysis of the protocol demonstrating its scientific soundness);
- risk analysis (a description and analysis of all increased risks to the research subjects and how these risks will be minimized; a justification for the investigation; and a description of the patient population including the number, age, sex, and condition);
- description of this device (a description of each important component, ingredient, property, and principle of operation of the device and any anticipated changes in the device during the investigation);
- monitoring procedures (the sponsor's written procedures for monitoring the investigation and the name and address of each monitor; see Chapter 4, "IDE Guidance and Policies", for a more detailed discussion);
- labeling (copies of all labeling for the device);
- consent materials (copies of all forms and materials given to subjects to obtain informed consent);
- IRB information (a list of the names, addresses, and chairpersons of all IRBs that will review the investigation and a certification of any action taken by them);
- other institutions (the name and address of any other institution not previously identified at which a part of the investigation may be conducted); and
- additional records and reports (a description of any records or reports of the investigation other than those required in Subpart G of the IDE regulation).

Report of prior investigations (812.27)

A report of prior investigations must include reports of all prior clinical, animal, and laboratory testing of the device. It should be comprehensive and adequate to justify the proposed investigation.

Specific contents of the report must include:

- a bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety and effectiveness of the device;

- copies of all published and unpublished adverse information;

- copies of other significant publications if requested by an IRB or FDA;

- a summary of all other unpublished information (whether adverse or supportive) that is relevant to an evaluation of the safety and effectiveness of the device; and

- if nonclinical laboratory data are provided, a statement that such studies have been conducted in compliance with the Good Laboratory Practice (GLP) regulation in 21 CFR Part 58. If the study was not conducted in compliance with the GLP regulation, include a brief statement of the reason for noncompliance.

FDA action on applications (812.30)

Approval or Disapproval. FDA will notify the sponsor in writing of the date it receives an IDE application. FDA may approve, approve with modification, or disapprove an IDE application. An investigation may not begin until **30** days after FDA receives the IDE application for the investigation of a device unless FDA notifies the sponsor that the investigation may not begin, or until FDA approves by order an IDE for the investigation. An investigation of a banned device may not begin until FDA approves by order an IDE for the investigation.

Grounds for Disapproval or Withdrawal. FDA may disapprove or withdraw approval of an IDE application if FDA finds that:

- the sponsor has not complied with applicable requirements of the IDE regulation, other applicable regulations, statutes, or any condition of approval imposed by an IRB or FDA;

- the application or report contains untrue statements or omits required material or information;

- the sponsor fails to respond to a request for additional information within the time prescribed by FDA;

- there is reason to believe that the risks to the research subjects are not outweighed by the anticipated benefits or the importance of knowledge to be gained; that the informed consent is inadequate; that the investigation is scientifically unsound; or that the device as used is ineffective; or

- it is unreasonable to begin or continue the investigation because of:

- ....the way the device is used, or

- ....the inadequacy of the investigational plans; the reports of prior investigations; the methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and installation of the device; or the monitoring and review of the investigation.

Notice of Disapproval or Withdrawal. If FDA disapproves an IDE application or proposes to withdraw approval, FDA will notify the sponsor in writing. A disapproval order will contain a complete statement of the reasons for disapproval and will advise the sponsor of the right to request a regulatory hearing under Part 16. FDA will provide an opportunity for a hearing before withdrawal of approval unless FDA determines that there is an unreasonable risk to the public health if testing continues.

Supplemental applications (812.35)

Supplemental applications are required for:

- **changes in the investigational plan** that may affect the scientific soundness of the investigation or the rights, safety, or welfare of the subjects. The sponsor is required to submit a supplemental application to FDA and obtain FDA approval for any such change and IRB approval when the change involves the rights, safety, or welfare of subjects. Prior FDA approval is not required for changes or deviations in the investigational plan to protect the life or physical well-being of a subject in an emergency. The sponsor must report such changes to FDA within 5 working days.

- **addition of new institutions or facilities**. The sponsor is required to submit:

  - ....certification of IRB approval;

  - ....information updating the IDE application, if the investigation is changed; and

  - ....a description of any modifications required by the IRB as conditions of approval. While submission of IRB approval is necessary, it is not a precondition for FDA's review of such a request.

Unless FDA specifically grants a waiver from these requirements, the sponsor may not begin the investigation at a new institution until:

- IRB approval is obtained;
- FDA receives certification of IRB approval; and
- FDA approves the supplemental application.

Confidentiality of data (812.38)

FDA will not disclose the existence of an IDE unless:

- FDA determines that the information had been previously disclosed to the public;
- FDA approves a PMA for a device subject to an IDE; or
- the device has in effect a Product Development Protocol (PDP) notice of completion.

Upon request, FDA will make publicly available a detailed summary of the information concerning the safety and effectiveness of the device that was the basis for approving, disapproving, or withdrawing approval of an application for an IDE for a banned device. FDA may also disclose a summary of selected portions of the safety and effectiveness data for public consideration of a specific pending issue.

Upon request of an individual or on its own initiative, FDA shall disclose a copy of a report of adverse device effects relating to that use. The availability for public disclosure of data and information in an IDE file shall be handled in accordance with section 814.9.

SUBPART C -- RESPONSIBILITIES OF SPONSORS

General responsibilities (812.40)

Sponsors are responsible for selecting qualified investigators and providing them with the information that they need to conduct the investigation properly. Proper monitoring of the investigation, ensuring IRB review and approval, submitting an IDE application, and informing the IRB and FDA promptly of any significant new information are also responsibilities of the sponsor.

FDA and IRB approval (812.42)

A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application.

Selecting investigators and monitors (812.43)

Selecting Investigators. A sponsor shall select investigators qualified by training and experience to investigate the device.

Control of Device. A sponsor shall ship investigational devices only to qualified investigators participating in the investigation.

Obtaining Agreements. A sponsor shall obtain from each participating investigator a signed agreement that includes:

- the investigator's curriculum vitae;

- where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience;

- if the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination; and

- a statement of the investigator's commitment to:

  -....conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;

  -....supervise all testing of the device involving human subjects; and

  -....ensure that the requirements for obtaining informed consent are met.

Selecting Monitors. A sponsor shall select monitors qualified by training and experience to monitor the investigational study in accordance with this part and other applicable FDA regulations. (FDA published a guideline on the monitoring of clinical investigations which is included in Chapter 4.)

Informing investigators (812.45)

A sponsor shall supply all investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device.

Monitoring investigations (812.46)

Securing Compliance. A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor shall also require that an investigator dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

Unanticipated Adverse Device Effects. A sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect.

A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor

makes this determination and not later than 15 working days after the sponsor first received notice of the effect.

Resumption of Terminated Studies. In the case of a significant risk device investigation, a sponsor may not resume a terminated investigation without IRB and FDA approval. For a non-significant risk device investigation, a sponsor may not resume a terminated investigation without IRB approval and, if the investigation was terminated for unanticipated adverse device effects [section 812.46(b)(2)], FDA approval.

SUBPART D -- IRB REVIEW AND APPROVAL

IRB composition, duties, and functions (812.60)

An IRB must comply with all applicable requirements of the IRB regulation (Part 56) and the IDE regulation (Part 812) in reviewing and approving device investigations involving human testing.

IRB Approval (812.62)

An IRB has the authority to review and approve, require modification, or disapprove an investigation. If no IRB exists or if FDA finds an IRB's review is inadequate, a sponsor may submit an application directly to FDA.

IRB continuing review (812.64)

An IRB must conduct its continuing review of an investigation in accordance with Part 56 (see Appendix D).

Reserved (812.65)

Significant risk device determination (812.66)

If an IRB determines that an investigation involves a significant risk device, it must notify the investigator and, if appropriate, the sponsor. The sponsor may not begin the investigation until approved by FDA as provided in section 812.30(a).

SUBPART E -- RESPONSIBILITIES OF INVESTIGATORS

General responsibilities of investigators (812.100)

An investigator is responsible for:

- ensuring that the investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations;

- protecting the rights, safety, and welfare of subjects; and
- control of the devices under investigation.

An investigator is also responsible for obtaining informed consent under Part 50 (see Appendix B). Additional responsibilities for maintaining and making reports are provided in Subpart G of the IDE regulation.

Specific responsibilities of investigators (812.110)

While awaiting approval of an IDE application, an investigator may determine whether or not potential subjects would be interested in participating in an investigation, but cannot request written informed consent or allow any subjects to participate before obtaining IRB and FDA approval.

Compliance. An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, the IDE regulation and other applicable FDA regulations, and any conditions of approval imposed by an IRB and FDA.

Supervising Device Use. An investigator shall permit use of the investigational device only with subjects under his/her supervision and shall not supply an investigational device to any person not authorized under the IDE regulation to receive it.

Disposing of Device. Upon completion or termination of a clinical investigation or the investigator's part of the investigation or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or dispose of the device as the sponsor directs.

Subpart F -- [Reserved]

SUBPART G -- RECORDS AND REPORTS

Records (812.140)

Investigator records. The following records must be maintained:

- all correspondence including required reports;
- records of receipt, use, or disposition of the investigational device;
- records of each subject's case history and exposure to the device;
- the protocol and documentation (date and reason) for each deviation from the protocol; and
- any records that FDA requires to be maintained by regulation or by specific requirement for a particular investigation.

Sponsor records. The following records must be maintained:

- all correspondence including required reports;

- records of shipment and disposition;

- signed investigator agreements;

- records concerning adverse device effects whether anticipated or not;

- any other records that FDA requires to be maintained by regulation or by specific requirement for a particular device or category of devices; and

- for a nonsignificant risk device investigation [section 812.140(b)(4)], consolidated in one location and available for FDA inspection:

  -....the name and intended use of the device;
  -....the objectives of the investigation;

  -....a brief explanation of why the device is not a significant risk device;

  -....the name and address of each investigator;

  -....the name and address of each IRB;

  -....the extent to which the good manufacturing practices (Part 820) will be followed (see Appendices E and F);

  -....records concerning adverse effects (whether anticipated or not) and complaints; and

  -....any other information required by FDA.

IRB Records. IRB records must be maintained in accordance with Part 56.

Retention Period. Investigators should maintain the required records for a period of **two** years after the date the investigation is completed or terminated or the records are no longer required to support a premarket approval application or a product development protocol. If an investigator or sponsor transfers custody of the records to another person, FDA must be notified within 10 working days after the transfer occurs.

Records Custody. An investigator or sponsor may withdraw from the responsibility to maintain records for the time required by transferring custody to another person who will accept responsibility for them.

Inspection (812.145)

FDA has authority to inspect facilities at which investigational devices are being held including any establishments where devices are manufactured, packed, installed, used, implanted, or where records of use are kept.

Sponsors, IRBs, and investigators are required to permit authorized FDA employees reasonable access at reasonable times to inspect and copy all records of an investigation. Upon notice, FDA may inspect and copy records that identify subjects.

Reports (812.150)

Investigator Reports. The following reports must be prepared:

- unanticipated adverse device effects -- as soon as possible but no later than 10 working days, and submitted to the sponsor and the reviewing IRB;

- withdrawal of IRB approval -- within 5 working days, and submitted to the sponsor;

- progress reports of the investigation -- at regular intervals but no less than yearly, and submitted to the sponsor, the monitor, and the reviewing IRB;

- deviations from the investigational plan - in an emergency, as soon as possible but no later than 5 working days after the emergency occurred, submit to the sponsor and the reviewing IRB; except in an emergency, prior approval from the sponsor is required and if the change or deviation may affect the scientific soundness of the investigational plan or the rights, safety or welfare of the subjects, the sponsor is required to obtain IRB approval and (for a significant risk device investigation) to submit to FDA a supplemental application and obtain FDA approval;

- use of the device without informed consent -- within 5 working days after the use occurs, and submitted to the reviewing IRB and the sponsor;

- final report -- within 3 months after termination or completion of the investigation, and submitted to the sponsor and the reviewing IRB; and

- other reports -- accurate, complete, and current information about any aspect of the investigation that the reviewing IRB or FDA may request.

Sponsor Reports. The following reports must be prepared:

- unanticipated adverse device effects -- within 10 working days after receiving notice of the adverse effect, and submitted to FDA and all reviewing IRBs and investigators;

- withdrawal of IRB approval -- within 5 working days of receipt of the withdrawal of IRB approval, and submitted to FDA and all reviewing IRBs and participating investigators;

- withdrawal of FDA approval -- within 5 working days after receipt of the notice of withdrawal of FDA approval, and submitted to all reviewing IRBs and participating investigators;

- current list of investigators with addresses -- every six months, and submitted to FDA for a significant risk device study;

- progress reports -- at regular intervals and at least yearly, and submitted to all reviewing IRBs. For a significant risk device, the sponsor shall also submit the progress report to FDA;

- recalls and device disposition -- within 30 working days after receipt of a request to return, repair, or dispose of an investigational device, and submitted to FDA and all reviewing IRBs;

- a final report - the sponsor must notify FDA and all reviewing IRBs within 30 working days of the completion or termination of a significant risk device investigation, and submit a final report to FDA and all reviewing IRBs and participating investigators within 6 months after the completion or termination of the investigation. For a nonsignificant risk device, the sponsor must submit a final report to all reviewing IRBs within 6 months after completion or termination.

- use of device without informed consent -- within 5 working days after receipt of notice of such use, and submitted to FDA;

- significant risk device determination -- within 5 working days of an IRB determination that the device is a significant risk device and not a nonsignificant risk device as proposed, and submitted to FDA; and

- other reports -- accurate, complete, and current information about any aspect of the investigation that FDA or the reviewing IRB may request.

3 HOW TO SUBMIT AN IDE

SUGGESTED FORMAT FOR IDE SUBMISSIONS
SUGGESTED ORIGINAL IDE APPLICATION ADMINISTRATIVE CHECKLIST
SUGGESTED CONTENT FOR ORIGINAL IDE APPLICATION COVER LETTER
SUGGESTED FORMAT FOR IDE PROGRESS REPORTS
COMMON PROBLEMS WITH ORIGINAL IDE APPLICATIONS

Chapter 3 covers information necessary to complete an investigational device exemption (IDE) application for submission to FDA. This includes filling out an IDE application, progress reports, and a checklist that is used for FDA administrative review. Any particular guidance you may need in submitting an IDE can either be found or referenced in Chapter 4.

A sponsor of a significant risk device study must submit a complete IDE application to FDA. FDA will not review an incomplete IDE submission (see IDE Refuse to Accept Procedures, IDE Memorandum #D94-1, in Chapter 4). There are no preprinted forms for an IDE application; however, an IDE application must include the information described in 812.20(b). The sponsor must demonstrate in the application that there is reason to believe that the risks to human subjects from the proposed investigation are outweighed by the anticipated benefits to subjects and the importance of the knowledge to be gained, that the investigation is scientifically sound, and that there is reason to believe that the device as proposed for use will be effective.

Included in this chapter are a suggested format and checklist for preparing IDE applications. An IDE submitter should consult these materials to ensure the completeness of the IDE submission. At the end of this chapter is a listing of the most common problems FDA encounters in its review of IDE applications.

For questions about the requirements of the IDE regulation and the Office of Device Evaluation s policies and procedures for the review of IDE applications, you may contact:

Director
Investigational Device Exemptions Program (HFZ-403)
Office of Device Evaluation
Center for Devices and Radiological Health
9200 Corporate Boulevard
Rockville, MD 20850
Telephone 301-594-1190

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SUGGESTED FORMAT FOR IDE SUBMISSIONS

In order to facilitate FDA's handling of IDE applications, the following recommendations are offered:

Use paper with nominal dimensions of 8 " by 11".

Use at least a 1 " wide left margin to allow for binding into jackets.

Use 3-hole punched paper to allow for binding into jackets.

If the submission exceeds 2" in thickness, separate into volumes and identify volume number.

Clearly and prominently identify submission as original IDE application or, for additional submissions to an IDE application, clearly identify the FDA assigned document number (e.g., G960000) and the type of submission (e.g., amendment or supplement) and the type of submission (e.g., Response to FDA letter; Addition of New Institution, etc.).

All copies of each submission must be identical.

Do not combine IDEs, PMAs and 510(k)s together; they must be separate submissions.

Unless the IDE sponsor has provided authorization in writing for another person to submit information on the sponsor's behalf, only the IDE sponsor may amend, supplement, or submit reports to the IDE.

Sequentially number the pages, providing a detailed table of contents, and use tabs to identify each section. This will help to facilitate the review of your submission.

All submissions, in triplicate, should be addressed to:

Food and Drug Administration
Center for Devices and Radiological Health
IDE Document Mail Center (HFZ-401)
9200 Corporate Boulevard
Rockville, MD 20850

Following is a suggested checklist that submitters may use to ensure that their original IDE application is administratively complete. The first section is a screening to determine whether an IDE application is required to be submitted to FDA. The next section is the information suggested to be included in the cover letter or cover page of the IDE application. Inclusion of this information should help speed our administrative processing of your application. The last section is a checklist to ensure that all the information required by regulation is addressed in the application.

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SUGGESTED ORIGINAL IDE APPLICATION ADMINISTRATIVE CHECKLIST

Following is a suggested checklist that submitters may use to ensure that their original IDE application is administratively complete. The first section is a screening to determine whether an IDE application is required to be submitted to FDA. The next section is the information suggested to be included in the cover letter or cover page of the IDE application. Inclusion of this information should help speed FDA s administrative processing of the application. The last section is a checklist to ensure that all the information required by regulation is addressed in the application.

Screening Information

Is an IDE application to FDA necessary?

1. Is the investigation within the categories exempt from the IDE regulation under section 812.2(c).....Yes__ No_

   (If yes, stop. IDE not required. IRB clearance and informed consent recommended, please check institution s policies.)

2. Is this a nonsignificant risk device investigation?.....Yes__ No__

   (If yes, stop. Submission to and approval from FDA not required. Follow abbreviated requirements (section 812.2(b)) including IRB approval and informed consent.) If the answer to both questions is no an IDE application must be submitted to FDA and approval must be obtained from both FDA and the IRB before the study may begin.

BASIC INFORMATION

Cover letter or title page should be provided with the following information:

Statement that submission is an original IDE application.

Sponsor Information - Must be located in United States (21 CFR 812.18(a)):

Name
Address
Contact Person
Telephone Number
Fax

Device Information:

Device Name
Intended Use

Manufacturer Information:

Name
Address
Contact Person
Telephone Number
Fax

Other Information:

Waiver Requests: Identify any requests for waivers and include a justification for the waiver.

Referenced Files: Identify any files included by reference. If files were not submitted by the sponsor, include a letter from the holder of the files which grants FDA permission to reference the files in its review of the current application.

Elements for an IDE Application

1. **Report of Prior Investigations (812.27):** Are the following items provided and are they comprehensive and adequate to justify the proposed investigation?

   a. report of all prior clinical, animal and laboratory testing.....Yes__ No_

   b. bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety and effectiveness of the device.....Yes__ No_

   c. copies of all published and unpublished adverse information.....Yes__ No_

   d. summary of all other unpublished information, whether adverse or supportive, that is relevant to an evaluation of safety and effectiveness of the device.....Yes__ No__

   e. statement whether nonclinical tests comply with the good laboratory practice (GLP) regulation in Part 58 .....Yes__ No_

      If any studies were not conducted in compliance with the GLP regulation, a brief statement of the reason for the noncompliance must be provided. Failure or inability to comply with this requirement does not justify failure to provide information on a relevant nonclinical test study.

   If any item is not provided, a justification for its omission must be provided.

2. **Investigational Plan (812.25):** Are the following items included, preferably in the

following order:

a. Purpose: Are the following clearly defined?

(1) name and intended use of the device.....Yes__ No_
(2) objectives of the investigation.....Yes__ No_
(3) duration of the investigation.....Yes__ No_
(specify in months and years)

b. Protocol: Are the following items provided and adequate?

(1) a written protocol describing the methodology to be used.....Yes__ No_
(2) an analysis of the protocol demonstrating its scientific soundness.....Yes__ No_

c. Risk Analysis: Are the following items provided and adequate to determine that the benefit and knowledge to be gained from the investigation outweigh the risks to the subjects?

(1) a description and analysis of all increased risks to the research subjects.....Yes__ No_
(2) the manner in which risks will be minimized.....Yes__ No_
(3) a justification for the investigation.....Yes__ No_
(4) a description of patient population, including number, age, sex and condition.....Yes__ No_

d. Description of the Device: Are the following items provided and adequate?

(1) a description of each important component, ingredient and property.....Yes__ No_
(2) the principle of operation of the device.....Yes__ No_
(3) a description of any anticipated changes in the device during the investigation.....Yes__ No_

e. Monitoring Procedures: Are the following items present?

(1) the written procedure for monitoring the investigation (see guidance on monitoring clinical investigations in Chapter 4).....Yes__ No_
(2) the name and address of the monitor.....Yes__ No_

If any item is not provided, a justification for its omission must be provided.

3. <u>Manufacturing Information:</u> Is adequate manufacturing information provided to allow a judgement about the quality control of the device (e.g., that the device will meet the intended specifications) based on the description of methods, facilities and controls used for:

a. manufacturing.....Yes__ No_
b. processing .....Yes__ No_
c. packing.....Yes__ No_
d. storage .....Yes__ No_
e. installation.....Yes__ No_

If any item is not provided, a justification for its omission must be provided.

4. <u>Investigator Information:</u> Are the following items complete?

a. example of investigator agreement [see 812.43(c)] which should include:

(1) the investigator's curriculum vitae;
(2) where applicable, a statement of the investigator's relevant experience (including the dates, location, extent and type of experience);
(3) if the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination; and
(4) a statement of the investigator's commitment to:
(i) conduct the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and FDA;
(ii) supervise all testing of the device involving human subjects; and
(iii) ensure that the requirements for obtaining informed consent are met.....Yes__ No_

b. certification that all participating investigators have signed the agreement and that no investigator will be added until the agreement is signed.....Yes__ No_

c. name and address of investigators who have signed the agreement.....Yes__ No_

If any item is not provided, a justification for its omission must be provided.

5. <u>IRB Information:</u>

a. Are the following items complete?

(1) name, address and chairperson of each IRB.....Yes__ No_
(2) certification of the action taken by each IRB, (i.e., approval).....Yes__ No_

b. How many IRBs have approved the investigation? _____

c. How many IRBs are currently reviewing the investigation or will review it in the future? _____

d. Names and addresses of any institutions (other than those identified above) where a part of the investigation may be conducted.....Yes__ No_

If any item is not provided, a justification for its omission must be provided.

6. <u>Sales Information:</u> Is the following information provided?

a. Is the device to be sold.....Yes__ No_
b. If yes, is the amount to be charged provided.....Yes__ No_
c. Explanation of why sale does not constitute commercialization .....Yes__ No_

812.7(b) prohibits the commercialization of an investigational device by charging subjects or investigators for a device a price larger than necessary to recover costs of manufacture, research, development, and handling.

If any item is not provided, a justification for its omission must be provided.

7. <u>Labeling:</u> Copies of all labeling for the device must be provided and must include the following:

a. Does the labeling contain the statement (required by 812.5(a)) "CAUTION- Investigational Device. Limited by Federal (or United States) Law to Investigational Use."....Yes__ No_

b. Does the labeling contain adequate information for the purposes of the investigation, in accordance with 812.5(a), including the name and place of business of the

manufacturer, packer, or distributor, the quantity of contents, and a description of all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions?.....Yes__ No_

If any item is not addressed, a justification for its omission must be provided.

c. Is the device being promoted as safe and effective for the use for which it is being investigated?.....Yes__ No_

812.7(d) prohibits the representation of an investigational device as safe and effective for the purposes for which it is being investigated.

8. <u>Informed Consent Materials:</u>

a. Are <u>all</u> forms and informational materials to be presented to the subject included?.....Yes__ No_

b. Does the informed consent form contain exculpatory language (see 21 CFR Part 50.20)?.....Yes__ No_

c. Does the informed consent form seek consent from the subject, if an adult, or a legal representative, if a minor.....Yes__ No_

d. Does the consent process involve a "short form" written consent (see 21 CFR Part 50.27(b)(2)).....Yes__ No__

e. Does the informed consent form contain the basic required elements? (see 21 CFR Part 50.25(a)).....Yes__ No__

<u>Required Elements:</u>

__ a statement that the study involves research

__ an explanation of the purposes of the research

__ the expected duration of the subject's participation

__ a description of the procedures to be followed

__ identification of any procedures which are experimental

__ a description of any reasonably foreseeable risks or discomforts to the subject

__ a description of any benefits to the subject or others

__ a disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject

__ a statement describing the extent to which confidentiality of the subject's records will be maintained and that FDA may inspect the records

__ an explanation as to whether any compensation and/or medical treatments are available if injury occurs and, if so, what they consist of or sources of further information

__ an explanation of whom to contact for answers to questions about the study and the subject's rights and whom to contact in the event of a research-related injury

__ a statement that participation is voluntary and that subjects may refuse to participate or discontinue participation at any time without penalty or loss of benefits

Additional Elements Required When Justified:

__ a statement that the procedure or treatment may involve unforeseeable risks to subject, or to the embryo or fetus if the subject were to become pregnant

__ anticipated circumstances under which the investigator may terminate the subject's participation without regard to the subject's consent

__ any additional costs to subject as a result of participation

__ consequences of a subject's decision to withdraw and procedures for withdrawal

__ a statement that significant new findings which may relate to the subject's willingness to participate will be provided to the subjects

__ the approximate number of subjects involved in the study

9. **Environmental Impact Assessment:** Is one of the following provided:

a. a claim for categorical exclusion from the requirement.....Yes__ No_

A categorical exclusion may be claimed by stating that "devices shipped under the Investigational Device Exemption are intended to be used for

clinical studies in which waste will be controlled or the amount of waste expected to enter the environment may reasonably be expected to be nontoxic" as provided for in 21 CFR 25.24(e)(7).

or

b. an environmental impact assessment (as described 21 CFR 25.31(a)) describing the potential environmental impact of manufacturing and investigating a device.....Yes__ No_

10. <u>Other Information:</u>

Provide additional information supportive of the investigation and any information FDA has identified (through previous contact with the agency or through guidance documents) as required.

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SUGGESTED CONTENT FOR ORIGINAL IDE APPLICATION COVER LETTER

Provide the following on the cover letter or cover page:

1. Statement that enclosed is an original IDE submission.

2. Device Information:

   a. Device Name
   b. Intended Use

3. Sponsor or agent - Must be located in United States (21 CFR 812.18(a)):

   Name
   Address
   Contact Person
   Telephone Number
   Fax

4. Manufacturer Information

   Name
   Address

Contact Person
Telephone Number
Fax

5. Applicant Information: may be other than the sponsor
(organization/individual making the submission, for example, consultant or lawyer)

6. If applicable, provide the following information:

   a. Pre-IDE/Pre-IDE meetings: Describe your contacts with the review division regarding this device. If a Pre-IDE was submitted, state the Pre-IDE number and name of FDA contact, if known, who reviewed the Pre-IDE. If a Pre-IDE meeting occurred, give name of FDA contact person and copy of meeting minutes.

   b. Waiver Requests: Identify any requests for waivers and include a justification for the waiver.

   c. Referenced Files: Identify any files included by reference (for example, approved PMA, 510(k), IDE, device or materials master file). If files were not submitted by the sponsor, include a letter from the holder of the files which grants FDA permission to reference the files in its review of the current application.

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SUGGESTED FORMAT FOR IDE PROGRESS REPORT

1. The Basics

- IDE Number
- Device name and indication(s) for use
- Sponsor's name, address and phone number, Fax
- Contact person

2. Study Progress
(Data from beginning of the study should be reported, unless otherwise indicated.)

- Brief summary of the study progress in relation to the investigational plan
- Number of investigators/investigational sites (attach list of investigators)
- Number of subjects enrolled (by indication or model)
- Number of devices shipped
- Brief summary of results
- Summary of anticipated and unanticipated adverse effects

- Description of any deviations from the investigational plan by investigators (since last progress report)

3. Risk Analysis

- Summary of any new adverse information (since the last progress report) that may affect the risk analysis; this includes preclinical data, animal studies, foreign data, clinical studies, etc.
- Reprints of any articles published from data collected from this study
- New risk analysis, if necessary, based on new information and on study progress

4. Other Changes

- Summary of any changes in manufacturing practices and quality control (including changes not reported in a supplemental application)
- Summary of all changes in the investigational plan not required to be submitted in a supplemental application

5. Future Plans

- Progress toward product approval, with projected date of PMA or 510(k) submission
- Any plans to change the investigation, e.g., to expand the study size or indications, to discontinue portions of the investigation or to change manufacturing practices (**NOTE**: Actual proposals for these changes should be made in a separate supplemental application).

Suggested Format for IDE Final Report

I. **The Basics**

IDE Number
Device name and indication for use
Sponsor's name, address and phone number, Fax
Contact person

II. **Study Progress**

(Data from beginning of the study should be reported, unless otherwise indicated.)

Brief summary of study progress in relation to investigational plan
Number of investigators/investigational sites (attach list of investigators)
Number of subjects enrolled (by indication or model)
Number of devices shipped
Disposition of all devices shipped

Brief summary of results
Summary of anticipated and unanticipated adverse effects
Description of any deviations from the investigational plan by investigators (since last progress report)

III. **Risk Analysis**

Summary of any new adverse information (since last progress report) that may affect the risk analysis; this includes preclinical data, animal studies, foreign data, clinical studies, etc.
Reprints of any articles published from data collected from this study

IV. **Other Changes**

Summary of any changes in manufacturing practices and quality control (including changes not reported in a supplemental application)
Summary of all changes in investigational plan not required to be submitted in a supplemental application

V. **Marketing Application or Future Plans**

Progress toward product approval, with date (or projected date) of PMA or 510(k) submission; or indication that marketing of device is not planned.
Any plans to submit another IDE application for this device or a modification of this device.

Annual Progress Reports and Final Reports

The IDE regulations do not specify the content of the annual progress or final reports. Therefore, the contents of these reports may largely be dictated by the sponsor. With respect to reports to the IRB, the IRB itself may specify what information it wishes to be included in these reports. Because FDA does require the information listed below, it is suggested that, at a minimum, the annual progress and final reports to the sponsor and the IRB also include the following items:

1. IDE number
2. Device name
3. Indications for use
4. Brief summary of study progress in relation to investigational plan
5. Number of investigators and investigational sites
6. Number of subjects enrolled
7. Number of devices received, used, and the final disposition of unused devices

8. Brief summary of results and conclusions
9. Summary of anticipated and unanticipated adverse device effects
10. Description of any deviations from investigational plan
11. Reprints of any articles published by the investigator in relation to the study

COMMON PROBLEMS WITH ORIGINAL IDE APPLICATIONS

Submitters should be sure to avoid the following deficiencies when submitting IDEs:

- premature IDE submissions;
- an inadequate report of prior investigations;
- an inadequate investigational plan; and
- an inadequate/incomplete design and manufacture.

Premature IDE submissions include:

- an inadequate characterization or description of the device and its operation;
- study objectives not defined;
- protocol not fully developed; and
- an incomplete risk analysis.

Another major deficiency is an inadequate report of prior investigations. A report of prior investigations must include reports of all prior clinical, animal, and laboratory testing of the device. It should be comprehensive and adequate to justify the proposed investigation. See 812.27 (in Appendix A) for regulations regarding reports of prior investigations. Examples of inadequate reports of laboratory studies include:

- inadequate description of methods;
- inadequate or no summary or conclusion; and
- conclusions not supported by data.

Examples of inadequate reports of animal studies include:

- no rationale for animal selection;
- no statistical justification for the number of animals selected; and
- inappropriate duration or follow-up.

Examples of inadequate reports of prior publications include:

- incomplete searches;
- copies of relevant publications not included;

- omission of adverse information; and
- failure to identify relevant parts or information and to summarize.

An inadequate investigational plan could include:

- questionable scientific soundness;
- failure to clearly develop or define study objectives;
- inadequate description of the protocol;
- failure to identify all risks identified; and
- failure to develop proper monitoring procedures.

See 812.25 (Appendix A) for regulations regarding investigational plans.

4 IDE GUIDANCE AND POLICIES

SIGNIFICANT AND NONSIGNIFICANT RISK DEVICE STUDIES - #D86-1
GOALS AND INITIATIVES FOR THE IDE PROGRAM - #D95-1
IDE REFUSE TO ACCEPT PROCEDURES - #D94-1
IMPLEMENTATION OF THE FDA/HCFA INTERAGENCY AGREEMENT REGARDING REIMBURSEMENT CATEGORIZATION OF INVESTIGATIONAL DEVICES - #D95-2
FEASIBILITY STUDIES - #D89-1
BIOLOGICAL EVALUATION OF MEDICAL DEVICES: THE USE OF ISO-10993 - #G95-1
PMA/510(K) EXPEDITED REVIEW PROCESS - #G94-2
SPONSOR RESPONSIBILITIES FOR A SIGNIFICANT RISK DEVICE INVESTIGATION
MONITORING OF CLINICAL INVESTIGATIONS
NOTICE OF AVAILABILITY OF INVESTIGATIONAL MEDICAL DEVICES
FDA INFORMATION SHEETS FOR IRBS AND CLINICAL INVESTIGATORS
WAIVER FOR ADDITIONAL INVESTIGATION SITES
EMERGENCY USE OF UNAPPROVED MEDICAL DEVICES
STATISTICAL GUIDANCE FOR CLINICAL TRIALS OF NON-DIAGNOSTIC MEDICAL DEVICES

The Office of Device Evaluation, CDRH, has developed the following guidance to clarify specific requirements of the IDE regulation. Many of the policies were developed in response to experience gained over the years with IDE applications. For additional information about any of the requirements of the IDE regulations, contact:

Director
Investigational Device Exemptions Program (HFZ-403)
Office of Device Evaluation
Center for Devices and Radiological Health
9200 Corporate Boulevard
Rockville, MD 20850
Telephone 301-594-1190

or

Division of Small Manufacturers Assistance (HFZ-220)
Office of Health and Industry Programs
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive
Rockville, MD 20850
Telephone 301-443-6597; 800-638-2041
Fax 301-443-8818

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SIGNIFICANT RISK AND NONSIGNIFICANT RISK MEDICAL DEVICE STUDIES
(FDA Information Sheets October 1, 1995; This replaces Bluebook Memorandum IDE Memorandum D86-1 (July 25, 1986) with the same title)

The Investigational Device Exemption (IDE) regulations (21 CFR Part 812) describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). An SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations (21 CFR Part 56) to identify certain studies that may be approved through an "expedited review" procedure. For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study (21 CFR Part 50).

Distinguishing Between SR and NSR Device Studies

The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations (21 CFR Part 812). NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the record keeping and reporting requirements. The SR/NSR decision is also important to FDA because the IRB serves, in a sense, as the FDA's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA.

If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA. If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, IRBs should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)].

SR/NSR Studies and the IRB

The NSR/SR Decision

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The IRB may ask the sponsor for information such as a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The IRB should ask the sponsor whether other IRBs have reviewed the proposed study and what determination was made. The sponsor should inform the IRB of the FDA's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor must notify FDA that a SR determination has been made. The study can be conducted at that institution as a SR investigation following FDA approval of an IDE application.

The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses a SR, an IRB must consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device. Two examples follow:

- The study of a pacemaker that is a modification of a commercially-available pacemaker poses a SR because the use of any pacemaker presents a potential for serious harm to the subjects. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison to the commercially-available model. The amount of potential reduced or increased risk associated with the investigational pacemaker should only be considered (in relation to possible decreased or increased benefits) when assessing whether the study can be approved.

- The study of an extended wear contact lens is considered SR because wearing the lens continuously overnight while sleeping presents a potential for injuries not normally seen with daily wear lenses, which are considered NSR.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the FDA does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the FDA will return the IDE application to the sponsor and the study would be presented to IRBs as an NSR investigation.

IRB and Sponsor Responsibilities Following SR/NSR Determination

If IRB decides the study is Significant Risk:

1. IRB Responsibilities:

    - Notify sponsor and investigator of SR decision
    - After IDE obtained by sponsor, proceed to review study applying requisite criteria (21 CFR 56.111)

2. Sponsor Responsibilities:

    - Submit IDE to FDA or, if electing not to proceed with study, notify FDA (CDRH Program Operations Staff 301-594-1190) of the SR determination;
    - Study may not begin until FDA approves IDE and IRB approves the study.
    - Sponsor and investigator(s) must comply with IDE regulations (21 CFR Part 812), as well as informed consent and IRB regulations (21 CFR Parts 50 and 56).

If the IRB decides the study is Nonsignificant Risk:

1. IRB proceeds to review study applying requisite criteria (21 CFR 56.111)

2. If the study is approved by the IRB, the sponsor and investigator must comply with

"abbreviated IDE requirements" [21 CFR 812.2(b)], and the Informed Consent and IRB regulations (21 CFR Parts 50 and 56).

The Decision to Approve or Disapprove

Once the SR/NSR decision has been reached, the IRB should consider whether the study should be approved or not. The criteria for deciding if SR and NSR studies should be approved are the same as for any other FDA regulated study (21 CFR 56.111). The IRB should assure that risks to subjects are minimized and are reasonable in relation to anticipated benefits and knowledge to be gained, subject selection is equitable, informed consent materials and procedures are adequate, and provisions for monitoring the study and protecting the privacy of subjects are acceptable. To assure that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation should be compared to the risks and benefits of alternative devices or procedures. This differs from the judgment about whether a study poses a SR or NSR which is based solely upon the seriousness of the harm that may result from the use of the device. Minutes of IRB meetings must document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

FDA considers studies of all significant risk devices to present more than minimal risk; thus, full IRB review for all studies involving significant risk devices is necessary. Generally, IRB review at a convened meeting is also required when reviewing NSR studies. Some NSR studies, however, may qualify as minimal risk [21 CFR 56.102(i)] and the IRB may choose to review those studies under its expedited review procedures (21 CFR 56.110).

Examples of NSR/SR Devices

The following examples are provided to assist sponsors and IRBs in making SR/NSR determinations. The list includes many commonly used medical devices. Inclusion of a device in the NSR category should not be viewed as a conclusive determination, because the proposed use of a device in a study is the ultimate determinant of the potential risk to subjects. It is unlikely that a device included in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

NONSIGNIFICANT RISK DEVICES

Low Power Lasers for treatment of pain (Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.)

Caries Removal Solution

Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions)

Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use

Conventional Gastroenterology and Urology Endoscopes and/or Accessories
Conventional Laparoscopes, Culdoscopes, and Hysteroscopes
Dental Filling Materials, Cushions or Pads made from traditional materials and designs
Denture Repair Kits and Realigners
Digital Mammography (Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.)
Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities)
Externally Worn Monitors for Insulin Reactions
Functional Electrical Neuromuscular Stimulators
General Biliary Catheters
General Urological Catheters (e.g., Foley and diagnostic catheters)
Jaundice Monitors for Infants
Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters
Menstrual Pads (Cotton or Rayon only)
Menstrual Tampons (Cotton or Rayon only)
Nonimplantable Electrical Incontinence Devices
Nonimplantable Male Reproductive Aids with no components that enter the vagina
Ob/Gyn Diagnostic Ultrasound within FDA approved parameters
Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain
Wound Dressings, excluding absorbable hemostatic devices and dressings (also excluding Interactive Wound and Burn Dressings)

SIGNIFICANT RISK DEVICES

GENERAL MEDICAL USE

Catheters:
- Urology - urologic with anti-infective coatings
- General Hospital - long-term percutaneous, implanted, subcutaneous and intravascular
- Neurological - cerebrovascular, occlusion balloon
- Cardiology - transluminal coronary angioplasty, intra-aortic balloon with control system

Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery, urological and dental applications
Surgical Lasers for use in various medical specialties
Tissue Adhesives for use in neurosurgery, gastroenterology, ophthalmology, general and plastic surgery, and cardiology

ANESTHESIOLOGY

Breathing Gas Mixers

Bronchial Tubes
Electroanesthesia Apparatus
Epidural and Spinal Catheters
Epidural and Spinal Needles
Esophageal Obturators
Gas Machines for anesthesia or analgesia
High Frequency Jet Ventilators greater than 150 BPM
Rebreathing Devices
Respiratory Ventilators
Tracheal Tubes

CARDIOVASCULAR

Aortic and Mitral Valvuplasty Catheters
Arterial Embolization Devices
Cardiac Assist Devices: artificial heart (permanent implant and short term use), cardiomyoplasty devices, intra-aortic balloon pumps, ventricular assist devices
Cardiac Bypass Devices: oxygenators, cardiopulmonary non-roller blood pumps, closed chest devices
Cardiac Pacemaker/Pulse Generators: antitachycardia, esophageal, external transcutaneous, implantable
Cardiopulmonary Resuscitation (CPR) Devices
Cardiovascular/Intravascular Filters
Coronary Artery Retroperfusion Systems
Coronary Occluders for ductus arteriosus, atrial and septal defects
Coronary and Peripheral Arthrectomy Devices
Extracorporeal Membrane Oxygenators (ECMO)
Implantable Cardioverters/Defibrillators
Laser Coronary and Peripheral Angioplasty Devices
Myoplasty Laser Catheters
Organ Storage/Transport Units
Pacing Leads
Percutaneous Conduction Tissue Ablation Electrodes
Peripheral, Coronary, Pulmonary, Renal, Vena Caval and Peripheral Stints
Replacement Heart Valves
RF Catheter Ablation and Mapping Systems
Ultrasonic Angioplasty Catheters
Vascular and Arterial Graft Prostheses
Vascular Hemostasis Devices

DENTAL

Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications
Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA)
Dental Lasers for hard tissue applications
Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants
Subperiosteal Implants
Temporomandibular Joint (TMJ) Prostheses

EAR, NOSE AND THROAT

Auditory Brainstem Implants
Cochlear Implants
Laryngeal Implants
Total Ossicular Prosthesis Replacements

GASTROENTEROLOGY AND UROLOGY

Anastomosis Devices
Balloon Dilation Catheters for benign prostatic hyperplasia (BPH)
Biliary Stints
Components of Water Treatment Systems for Hemodialysis
Dialysis Delivery Systems
Electrical Stimulation Devices for sperm collection
Embolization Devices for general urological use
Extracorporeal Circulation Systems
Extracorporeal Hyperthermia Systems
Extracorporeal Photopheresis Systems
Femoral, Jugular and Subclavian Catheters
Hemodialyzers
Hemofilters
Implantable Electrical Urinary Incontinence Systems
Implantable Penile Prostheses
Injectable Bulking Agents for incontinence
Lithotripters (e.g., electrohydraulic extracorporeal shock-wave, laser, powered mechanical, ultrasonic)
Mechanical/Hydraulic Urinary Incontinence Devices
Penetrating External Penile Rigidity Devices with components that enter the vagina
Peritoneal Dialysis Devices

Peritoneal Shunt
Plasmapheresis Systems
Prostatic Hyperthermia Devices
Urethral Occlusion Devices
Urethral Sphincter Prostheses
Urological Stints (e.g., ureteral, prostate)

GENERAL AND PLASTIC SURGERY

Absorbable Adhesion Barrier Devices
Absorbable Hemostatic Agents
Artificial Skin and Interactive Wound and Burn Dressings
Injectable Collagen
Implantable Craniofacial Prostheses
Repeat Access Devices for surgical procedures
Sutures

GENERAL HOSPITAL

Implantable Vascular Access Devices
Infusion Pumps (implantable and closed-loop - depending on the infused drug)

NEUROLOGICAL

Electroconvulsive Therapy (ECT) Devices
Hydrocephalus Shunts
Implanted Intracerebral/Subcortical Stimulators
Implanted Intracranial Pressure Monitors
Implanted Spinal Cord and Nerve Stimulators and Electrodes

OBSTETRICS AND GYNECOLOGY

Antepartum Home Monitors for Non-Stress Tests
Antepartum Home Uterine Activity Monitors
Catheters for Chorionic Villus Sampling (CVS)
Catheters Introduced into the Fallopian Tubes
Cervical Dilation Devices
Contraceptive Devices:
- Cervical Caps
- Condoms (for men) made from new materials (e.g., polyurethane)
- Contraceptive In Vitro Diagnostics (IVDs)
- Diaphragms

Female Condoms
Intrauterine Devices (IUDs)
New Electrosurgical Instruments for Tubal Coagulation
New Devices for Occlusion of the Vas Deferens
Sponges
Tubal Occlusion Devices (Bands or Clips)
Devices to Prevent Post-op Pelvic Adhesions
Embryoscopes and Devices intended for fetal surgery
Falloposcopes and Falloposcopic Delivery Systems
Intrapartum Fetal Monitors using new physiological markers
New Devices to Facilitate Assisted Vaginal Delivery
Thermal Systems for Endometrial Ablation

OPHTHALMICS

Class III Ophthalmic Lasers
Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in the eye using new active agents or preservatives with no history of prior ophthalmic/contact lens use or not generally recognized as safe for ophthalmic use
Corneal Implants
Corneal Storage Media
Epikeratophakia Lenticulas
Extended Wear Contact Lens
Eye Valve Implants (glaucoma implant)
Intraocular Lenses (IOLs) [21 CFR part 813]
Keratoprostheses
Retinal Reattachment Systems: fluids, gases, perfluorocarbons, perfluorpropane, silicone oil, sulfur hexafluoride, tacks
Viscosurgical Fluids

ORTHOPEDICS AND RESTORATIVE

Bone Growth Stimulators
Calcium Tri-Phosphate Hydroxyapatite Ceramics
Collagen and Bone Morphogenic Protein Meniscus Replacements
Implantable Prostheses (ligament, tendon, hip, knee, finger)

RADIOLOGY

Boron Neutron Capture Therapy
Hyperthermia Systems and Applicators

Your comments and suggestions for additional examples are welcome and should be sent to:

Program Operation Staffs (HFZ-403)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850
(301) 594-1190

*** ***

GOALS AND INITIATIVES FOR THE IDE PROGRAM (7/12/95) IDE MEMORANDUM - #D95-1

Purpose

The purpose of this memorandum is to establish procedures for the efficient review of IDEs and to identify performance goals for the IDE Program.

Background

The Office of Device Evaluation (ODE) has traditionally approved approximately one third of the original investigational device exemption (IDE) applications in the first 30 day review cycle. In recent times (fiscal years (FY) 1993 and 1994), however, only 25% of the original IDE applications were approved during this initial review period. In addition, the average total time from receipt of the application to approval increased to 242 days after averaging 178 days for the last 5 years.

The reasons for non-approval may be summarized as relating to inadequate characterization of the device being investigated, poorly designed clinical trials, and inadequate subject protection measures. In all cases, ODE's intent has been to improve the quality of the information derived from the investigations and to protect the well-being of those participating in the clinical trials. We must recognize, however, that our approach has had some unintended effects such as discouraging the conduct of the clinical trials and thus the generation of potentially useful information or causing the trials to be conducted outside the United States without guidance from FDA. ODE staff has also been expending considerable resources in reviewing multiple amendments over an extended period of time.

If the performance goals presented below are achieved, the gain to be realized by both the regulated industry and ODE staff would be significant. Increasing the approval rate and reducing the time to approval for original IDEs to more reasonable levels will encourage the medical device industry to conduct their clinical investigations in the United States (U.S.) rather than overseas. If the clinical trials are conducted domestically, and thus with FDA guidance, the quality of the trials and the data generated from them should be more congruent with premarket approval requirements than if the investigations were conducted overseas without input from FDA review. In addition, the data resulting from the domestic trials will be representative of medical practice in the U.S. Thus, the review process for the marketing applications should proceed more expeditiously, saving time and resources for the regulated industry and FDA. Finally, if the device trials are conducted here, U.S. physicians will have earlier access to and experience with these new technologies, while U.S. patients participating in the trials will also have the potential benefit of these novel therapies.

Below, the performance goals for the IDE Program and the initiatives to be implemented to help reach these goals are presented.

1) During FY95, increase the approval rate for original IDEs from its current rate of 27% (FY94) to approximately 66% in the first 30 day review cycle, especially for those submissions for which there was FDA-Industry interaction during the process (e.g., pre-IDE meetings, submissions, etc.).

2) During FY95, reduce the average number of review cycles to approval to less than two cycles. Currently, more than two amendments per IDE are required before approval of the application. Thus, at least three review cycles are generally required before the initiation of a device clinical trial.

Procedures

In order to help ODE's reviewing divisions reach these performance goals, the following initiatives will be implemented.

1) **Pre-IDE meetings.** Sponsors should be encouraged to meet with ODE staff before the IDE application is submitted for review. Meeting with the regulated industry before the IDE application is submitted should serve to increase the sponsor's understanding of various FDA requirements, regulations, and guidance documents and thus lead to more complete original IDE applications. (See attached policy entitled, "Procedures for Pre-IDE Meetings and Submissions.")

2) **Pre-IDE applications.** Sponsors should be encouraged to submit preliminary information for ODE review before making the formal IDE submission. Sponsors should submit those sections of the IDE application for which they require FDA guidance (e.g., clinical protocol

design, pre-clinical testing, etc.) while preparing the remainder of the IDE submission. This will allow ODE staff to provide informal guidance to the industry on troublesome parts of the IDE application before the official submission is made. In addition, since this informal review will be conducted while other parts of the application are being prepared, it should not extend the total preparation time for the IDE application. (See attached policy entitled, "Procedures for Pre-IDE Meetings and Submissions.")

3) **An interactive review process.** By communicating frequently with industry during the review process, rather than only at the completion of the review, deficient information can be addressed within fewer review cycles. This would be of significant benefit to both industry and ODE staff. ODE reviewers, with the concurrence of their supervisors, should feel free to use the telephone or telefacsimile to aid in the interactive review. Documentation of this communication must be included in the IDE record, and hardcopies of information transmitted by telefacsimile must be logged into the IDE database. (See attached policy entitled,"IDE Telefacsimile Policy.")

4) **Use of new strategies in the clinical development of devices.** If the original IDE application does not support the initiation of the substantive (pivotal) clinical trial, ODE staff should consider the use of feasibility/pilot studies. Such trials may be used to: provide investigators with initial device experience; help address specific safety concerns; permit initial assessment of device design; better define the clinical endpoints, success/failure criteria, the intended patient population, and appropriate follow-up period; assess the therapeutic effect of the device and estimate the required patient population size; and clarify the possible medical claims before the multi-centered trial is initiated. The type of device, the risks posed by the device, what is known about these risks, and the questions to be addressed in the limited study must all be considered when deciding whether a feasibility/pilot study is appropriate, and if so, the size of the study. Thus, the use of this type of strategy in the conduct of clinical trials not only permits a trial which may have otherwise been disapproved to be initiated on a limited basis but also provides for a better designed substantive trial for the marketing application.

Procedures for Pre-IDE Meetings and Submissions

In order to facilitate the initiation of clinical trials under the Investigational Device Exemptions (IDE) regulations, FDA is encouraging sponsors to begin communicating with the reviewing division prior to the submission of the original IDE application. This communication may take the form of a "Pre-IDE" meeting and/or a Pre-IDE submission. Pre-IDE meetings should occur early in the IDE preparation process so that any advice/guidance provided by ODE staff can be used in the development of supporting pre-clinical data or incorporated into the IDE application. These meetings may take the form of telephone conference calls, video conferences, or face-to-face

discussions. In addition to the general requirements set forth in Blue Book Memorandum #I89-3, "Meetings with the Regulated Industry," and #I93-1, "Telephone Communications Between ODE Staff and Manufacturers," the following requirements apply specifically to the IDE program. All pre-IDE meetings should be recorded by the division and reported on a quarterly basis to senior ODE management. Minutes of the meeting should include the date of the meeting, the attendees (FDA and industry), whether material was submitted prior to the meeting for discussion/review by ODE staff, a summary of the discussion, and any recommendations or guidance provided by FDA.

Pre-IDE submissions may consist of a draft clinical protocol, a proposal for pre-clinical testing, pre-clinical test results, or other information for which the sponsor wishes to obtain preliminary FDA review and comment in order to facilitate the IDE application process. Pre-IDE submissions may also consist of protocols for foreign studies when the studies will be used to support future marketing applications to be submitted to FDA.

Pre-IDE submissions will receive the same confidentiality of data and information as provided for IDE applications under 21 CFR 812.38. Therefore, FDA will not disclose the existence of a pre-IDE submission unless its existence has previously been publicly disclosed or acknowledged, until FDA approves an application for marketing approval of the device subject to this submission.

Pre-IDE submissions must be recorded and tracked, and so should be submitted in triplicate to the Document Mail Center (DMC) for processing. The DMC will assign the document a Pre-IDE number (PIDE), record it in the Pre-IDE logbook, and forward it to the appropriate division for review. (At this time, the IDE database cannot track Pre-IDE submissions.) If a Pre-IDE submission is received by the division without going through the DMC, the division is responsible for taking the document to the DMC so that it can be properly processed. At the time of log-in, the document mail clerk will also record the dates of submission and receipt, the sponsor's name, the name of the device, and the division to which it is assigned. The Pre-IDE number will be recorded on the top right corner of the submission, just as is done for official IDE applications.

Since the IDE database base cannot track Pre-IDEs, the divisions will be responsible for tracking the submissions and ensuring that a timely response is issued. A Pre-IDE boilerplate acknowledgment letter is available on the LAN (P-01) and should be sent to the sponsor upon receipt of the Pre-IDE submission. This letter indicates that FDA will attempt to provide a response to the sponsor in a timely manner, usually within 60 days of receipt. ODE's response may take the form of a written letter, or comments may be provided in a meeting or during a telephone conference call. Whichever method of response is used, it should be documented in the Pre-IDE file. (A copy of the letter, meeting minutes, or memorandum of the telephone conversation should be securely attached to the Pre-IDE submission.) There is a shelf in DMC where Pre-IDE submissions may be stored.

When the original IDE application is submitted, the division must note in the comments section of the IDE Tracking Sheets the Pre-IDE number assigned by the DMC if a Pre-IDE had been

reviewed for this submission. This will allow a method of connecting the Pre-IDE to the original IDE application.

IDE Telefacsimile Policy

General guidance for the acceptance of telefacsimile (FAX) telecommunications is provided in ODE's Blue Book Memorandum #I90-3 "Document Control Procedures." In this memorandum, it is stated that "As a general rule, information and data required to review and reach a decision on a submission may not be accepted via fax." In addition, according to the IDE regulations [21 CFR 812.20(a)(3)], all correspondence concerning an application or a supplemental application must be submitted by registered mail or by hand. The intent of this section of the regulations was to ensure that in order for information to be considered an official part of the IDE file, that information must be submitted in writing. At the time the IDE regulations were developed, however, the technology which permits communication via telefacsimile did not exist. Therefore, ODE has requested an official ruling from the Office of General Counsel on the acceptability of FAXED information, i.e., the need for a follow-up hardcopy. Until a definitive response is received, the policy presented below will serve as the official IDE FAX policy for the Office.

As stated above, past Office policy regarding use of FAXED information, as outlined in Blue Book Memorandum #I90-3 and as amplified in a February 17, 1994 memorandum by ODE's Integrity Officer, dictated that FAXED information could be used for purposes such as to facilitate the exchange of ideas and clarify points of discussion but could not serve as the basis of a decision without a confirmatory hardcopy. While the above policy statements remain in effect, ODE is encouraging more liberal use of the FAX machine as an aid to resolving deficiencies in the IDE application. Thus, a sponsor could submit information addressing deficiencies in areas such as the pre-clinical testing, the investigational plan, the risk analysis, the informed consent document, manufacturing procedures, etc., which had previously been discussed by phone with the reviewer. Although a follow-up hardcopy of the FAXED information still needs to be added to the administrative record and thus must be submitted to the Document Mail Center (DMC), early receipt of the information by FAX should permit a more expeditious review of the information and resolution of the deficiencies.

A follow-up hardcopy of the FAXED information should be received in the DMC by the 30th day of the review cycle so that it can be properly logged in as an IDE amendment. Therefore, reviewers must notify the sponsor that any information which is FAXED to ODE must also be sent in triplicate by overnight mail to the DMC for receipt by the next business day. If multiple FAXes are received by the division during the course of the review, hardcopies of all of the information may be submitted in one mailing rather than after each individual FAX. When the follow-up hardcopies are received by the DMC, one copy will be added to Copy 1 of the IDE file and one copy will be forwarded to the division for verification that the hardcopy is in fact a duplicate of the FAXED information. The hardcopy and a note stating that the hardcopy is a duplicate of the previously received FAX should be added to the file by the reviewer. The third

copy of the hardcopy is the reviewer's deskcopy and can be added to Copy 3 of the IDE file or discarded.

If the follow-up hardcopy is expected to arrive after day 30, reviewers must FAX the Duplicate Information Sheet (see attachment) to the sponsor. This sheet is to be used as a cover sheet to the hardcopy to ensure that when the information is received by the DMC, it will be correctly logged in as an IDE amendment to the original IDE application rather than as a supplement. Subsequent processing of the hardcopy will be as above.

See next page for facsimile cover sheet.

Fax

Duplicate

IDE Number:_____

I certify that the information contained in this submission is an exact duplicate of information which was previously provided by telefacsimile on the date(s) listed below. (That is, no new information which has not been previously provided is contained in this submission.)

Submitted by: _____ _____
(Name) (Signature and date)

_____
(Title)

_____
(Company Name)

_____
(Street Address)

_____
(City, State and Zip Code)

_____
(Phone Number)

*** ***

IDE REFUSE TO ACCEPT PROCEDURES (5/20/94) IDE MEMORANDUM #D94-1

Purpose

The purpose of this memorandum is to establish procedures under which an IDE that does not meet a minimum threshold of acceptability will not be accepted for substantive review and approval.

Background

The Office of Device Evaluation (ODE) receives approximately 225 original Investigational Device Exemptions (IDE) submissions each year. Many of these applications are incomplete or grossly inadequate, i.e., they fail to contain information clearly required under the regulations and they fail to contain the components necessary to allow substantive review. An IDE application that is missing any of the elements of 21 CFR 812.20, is technically an incomplete application and, therefore, not subject to the 30 day review clock. As a means to employ ODE resources more effectively, these procedures are being implemented to ensure that IDEs meet a minimum threshold of acceptability; otherwise, ODE will refuse to accept the application. These procedures will benefit both FDA and IDE sponsors.

A primary goal in establishing these "Refuse to Accept Procedures" for IDEs is to improve the use of our review resources by ensuring that they are focused on the review of reasonably complete and well-supported applications. Often, during initial substantive review, ODE has found that crucial information necessary to make a decision to approve or disapprove an IDE has been omitted. When making a decision to accept or not to accept an application, ODE will identify those applications in which sufficient information is submitted to allow a decision on the approvability of the investigation (i.e., the application is complete on its face). By establishing these procedures with criteria for completeness of an application that are clear, consistent, and available to sponsors, they will know what is expected of them for each submission and device they intend to investigate. Sponsors will be likely to comply with the established criteria to speed the time to substantive review of and a final decision on their application.

These procedures are based upon the Management Action Plan (MAP) initiative issue paper entitled "Center for Devices and Radiological Health's Investigational Device Exemptions (IDE) Refuse to Accept Policy." This Blue Book Memorandum embodies the guidance procedures flowing from that issue paper and hereby replaces that document as the policy of ODE. Attached to the MAP issue paper was a document entitled "IDE Refuse to Accept Criteria" and an accompanying checklist. As described below, these criteria and the checklist will be used by ODE reviewers in applying these guidance procedures to the review of incoming IDEs.

In general, there are three bases for refusal to accept an IDE:

1. An approved IDE is not required for the investigation.

2. The application omits a section of the IDE required under the IDE regulation, 21 CFR Part 812.

3. The application fails to address generally accepted scientific and professional principles governing the conduct of clinical trials or scientific/technical issues clearly described in general, device-specific, and crosscutting guidance documents made publicly available by FDA.

The checklist that accompanies the "IDE Refuse to Accept Criteria" is a general checklist. Divisions may modify or supplement this general checklist based on available guidance documents appropriate to their specific device areas. Division guidance documents should be promulgated wherever needs are identified. Guidances should provide specific details about what is expected and acceptable for all components of the submissions. Each product specific guidance should include a checklist to be used by a) the applicant in preparing the submission and b) reviewers during the initial evaluation to consider accepting the application for full review. Checklists should also be prepared for existing guidelines. This will save time and provide consistency across submissions. Also, emphasis should be placed on improved communication with industry.

In addition to the copies that are being made available to ODE reviewers, the document, "IDE Refuse to Accept Criteria" and any device specific guidance documents and checklists developed by the divisions are being made available to manufacturers and other members of the public by the Center's Division of Small Manufacturers Assistance.

Procedures

This guidance memorandum will be implemented by the review divisions within the Office of Device Evaluation utilizing the following procedures. The specific timeframes are goals that will be met to the extent permitted by available resources.

1. Processing

   a. The ODE Document Mail Center (DMC) will log in and jacket the IDE and forward it to the IDE Staff. The IDE Staff will conduct a preliminary review to verify that the submission is an IDE, and that it is administratively complete. If grossly administratively incomplete, the IDE Staff will issue an incomplete letter. If the submission is administratively complete, it will be forwarded to the appropriate review division within 2 days of receipt of the application in the DMC or as quickly as available resources allow.

   b. A designated reviewer (Branch Chief, Reviewer, CSO, CST), using the IDE Refuse to

Accept Criteria and checklist, and other appropriate device specific checklists, will determine whether the IDE is sufficiently complete to allow substantive review. The division should consult with the Program Operations Staff (POS) on any decision that is particularly difficult or controversial.

c. Refuse to Accept recommendation(s) will be forwarded to the appropriate supervisor for concurrence within 10 days of DMC's receipt.

d. If an application is found to be sufficiently complete to allow substantive review, the IDE will be placed into the queue for substantive review.

e. If an application is found to be insufficiently complete to allow substantive review, a Refuse to Accept letter will be prepared, in coordination with the POS Staff, for the Division Director's signature. The Refuse to Accept letter, detailing the omissions or inadequacies that led to the decision not to accept the application, will issue within 15 days of receipt of the original IDE. The letter will clearly state whether a complete, new application must be submitted or specify which portion of the application must be provided if the sponsor wishes to pursue the investigation.

2. Industry Inquiries

In the event that the sponsor has questions regarding the Refuse to Accept letter, the sponsor may contact the appropriate Division Director, via letter, telephone, or telefax, regarding the decision.

3. Monitoring

The implementation of the IDE Refuse to Accept Procedures will be reviewed by the Office of the Director, ODE, at regular intervals, approximately every 90 days, to determine the number of incomplete and/or inadequate applications not accepted, the consistency with which the criteria are applied among and within divisions, further necessary refinements to the process, and the overall impact on the IDE program.

Filing Review Elements	Yes Present Omission Justified	No Inadequate Omitted

ORIGINAL IDE CHECKLIST FOR ADMINISTRATIVE REVIEW

Filing Review Elements	Yes Present Omission Justified	No Inadequate Omitted
I. Screening Information **F. Is the investigation within the categories of investigations that are not exempt from the IDE regulation under 812.2(c)?**		
G. Is this a significant risk device investigation? (21 CFR 812.3(m) and 812.20(a)(1)		
H. If there has been an Integrity Investigation, has the ODE integrity officer given permission to proceed with review? (If no integrity investigation, check yes)		
I. U.S. sponsor, address, telephone number and contact person identified (Note: IDE application will not be approved without a U.S. sponsor) (21 CFR 812.18(a))		
II. Format for submission **A. Table of contents (21 CFR 812.20(b)**		
B. Submission clearly paginated		
C. 3 copies included (21 CFR 812.20(a)(3))		
III. Required elements for application **A. Report of prior investigations (Are the following items present in the application?) (21 CFR 821.27)**		

Filing Review Elements	Yes Present Omission Justified	No Inadequate Omitted
4. Report of clinical, animal and laboratory testing		
5. Bibliography of all relevant publications		
6. Copies of published and unpublished adverse information		
7. Summary of all other unpublished information		
8. Statement whether nonclinical tests comply with GLP regulation or justification for noncompliance		
B. Investigational Plan (32 CFR 812.25)		
1. Purpose: Are the following items clearly defined?		
d. Name and intended use of the device		
e. Objectives of the investigation		
f. Duration of the investigation (Example: specify-months and years)		
2. Protocol: Are the following items present?		
a. Written protocol describing methodology including:		
i. objectives, hypothesis to be tested, or question to be answered		
ii. description of the type of trial (i.e., controlled/open, double-blind/single-blind, etc.)		
iii. detailed description of the conduct of the trial		

Filing Review Elements	Yes Present Omission Justified	No Inadequate Omitted
iv. description of statistical methods		
v. case report forms		
3. Risk Analysis: Are the following items present in the application?		
a. Description and analysis of all risks to subjects		
b. Justification for the investigation		
4. Description of the Device: Are the following items present?		
a. Description of each important component, ingredient and property		
b. Principle of Operation		
c. Copies of all labeling for the device		
5. Monitoring Procedures: Are the following items present?		
a. Written procedures		
b. Name and address of the individual(s) who will monitor the study		
C. Manufacturing Information [21 CFR 812.20(b)(3)]: Does the application contain a description of methods, facilities and controls used for:		
1. Manufacturing		
2. Processing		
3. Packing		
4. Storage		

Filing Review Elements	Yes Present Omission Justified	No Inadequate Omitted
5. Installation		
D. Investigator Information [21 CFR 812.20(b)(4)] Are the following items included?		
1. Example of investigator agreement in accordance with 21 CFR 812.43(c)		
2. Certification that all participating investigators will or have signed the agreement and that no investigator will be added until the agreement is signed (21 CFR 812.29(b)(5)		
E. Sales information [21 CFR 812.7(b)]: Is the following information provided?		
1. Is the device to be sold?		
2. Explanation of why sale does not constitute commercialization		
F. Labeling [21 CFR 812.5] **Is a sample of the proposed labeling complete and included in the submission?**		
G. Informed Consent Materials [21 CFR 50.20 and 812.25(g)]: **Are <u>all</u> forms and informational materials to be presented to the subjects submitted?**		
H. Environmental Impact Assessment [21 CFR 25.31 and 812.20(b)(9)]: Has the sponsor provided:		
1. An environmental impact assessment describing the potential environmental impact of manufacturing and		

Filing Review Elements	Yes Present Omission Justified	No Inadequate Omitted
investigating a device		
2. A claim for categorical exclusion from the requirement		

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IMPLEMENTATION OF THE FDA/HCFA INTERAGENCY AGREEMENT REGARDING REIMBURSEMENT CATEGORIZATION OF INVESTIGATIONAL DEVICES (9/15/95) IDE MEMORANDUM - #D95-2

Purpose

The purpose of this memorandum is to establish procedures for fulfilling FDA's responsibilities as defined in the FDA/HCFA Interagency Agreement (IA) pertaining to the reimbursement of investigational devices.

Background

According to the statute governing the Medicare program (Section 1862 (a)(1)(A) of the Social Securities Act), the Health Care Financing Administration (HCFA) is permitted to reimburse for medical services and products that are deemed "reasonable and necessary" for the diagnosis or treatment of an illness or injury, or to improve the functioning of a malformed body member. The Medicare program has historically interpreted the statutory terms "reasonable and necessary" to mean that a service or medical device must be safe and effective, medically necessary and appropriate, and not experimental in order to qualify for reimbursement. For Medicare coverage purposes, the term "experimental" has been used synonymously with the term "investigational." Therefore, with rare exception, an FDA-approved Investigational Device Exemption (IDE) application served as an indication that the device was not "reasonable and necessary" within the meaning of the Medicare program. Thus, Medicare coverage was denied for devices which were under an IDE and had not yet received premarket notification clearance and or premarket approval.

There is increasing recognition, however, that there are devices which are refinements of existing technologies or replications of existing technologies made by other manufacturers. Many of these devices are under an FDA-approved IDE as a means of gathering the scientific information needed for FDA to establish the safety and effectiveness of that particular device, even though there is evidence that the device type can be safe and effective. Such devices could be viewed as "reasonable and necessary" by Medicare and thus be reimbursed if it were possible to identify these devices to HCFA.

On September 8, 1995, FDA and HCFA entered into an Interagency Agreement (See Attachment A) pursuant to which FDA agreed to institute a procedure for providing certain information to HCFA to aid in its reimbursement decisions. The information supplied to HCFA will be used in determining whether sufficient information exists concerning the safety and effectiveness of the investigational device to permit reimbursement under the Medicare program. Specifically, FDA will inform HCFA whether the clinical evaluation of an investigational device falls into one of two categories.

Those investigations involving innovative devices believed to be in Class III for which "absolute risk" of the device type has not been established (i.e., initial questions of safety and effectiveness have not been resolved and thus FDA is unsure whether the device type can be safe and effective) will be assigned to Category A. Devices believed to be in Classes I or II or devices believed to be in Class III where the incremental risk is the primary risk in question (i.e., underlying questions of safety and effectiveness of that device type have been resolved) will be assigned to Category B. Thus, Category B includes those device types known to be safe and effective because, for example, other manufacturers have obtained FDA approval/clearance for that device type. The precise criteria to be used by FDA in assigning IDEs to these reimbursement categories are set forth in the Interagency Agreement.

This interagency effort is an important initiative which will significantly impact both patient care and the development of new medical technology. By expanding the Medicare coverage policy to include certain investigational devices, Medicare beneficiaries will be assured greater access to the latest advancement in medical technology. In addition, the revision of the reimbursement policy to include investigational devices may help to improve the quality of clinical studies by ensuring that the Medicare patient population is included in the investigations and thus the devices are being tested on the appropriate patient population. Finally, it is anticipated that this change in policy will help to facilitate patient enrollment into clinical trials. Implementation of FDA's responsibilities as defined in the Interagency Agreement will help attain these important goals.

Procedures

Below, the procedures to be used by ODE staff in order to fulfill FDA's responsibilities in the Interagency Agreement are described. Implementation of the IA will involve two phases. In phase I, all IDE applications that are either approved, conditionally approved, or deemed approved (unless deemed approved and immediately withdrawn) by September 15, 1995 will be assigned to one of the two reimbursement categories as described in the Interagency Agreement. Phase II of the process will begin on September 18, 1995. On this date, each reviewing division, as a routine part of the IDE review process, will assume responsibility for implementing the reimbursement categorization process for all IDEs that are received on or after that date. Each of these phases is discussed in detail below.

A. Phase I: Categorization of Approved IDEs

Using the criteria defined in the attachment of the Interagency Agreement, the divisions will be responsible for categorizing all IDEs which are approved ("full", conditional, or deemed) by September 15, 1995. A special training session will be conducted by ODE senior management and the IDE staff during which guidance on the categorization determination process will be provided to division supervisors (branch chiefs and associate/deputy division directors). In most instances, it will be possible to categorize the investigational device based on data available in the

IDE database; however, in some instances, it may be necessary to refer to the actual IDE application as well as information regarding similar marketed devices. It is anticipated that the vast majority of devices will be assigned to Category B (i.e., Non-experimental/Investigational). The data on reimbursement categorization will be compiled and forwarded to HCFA on or before November 1, 1995. Therefore, the categorization of all IDEs approved by September 15, 1995 must be completed and forwarded to the IDE staff no later than October 6, 1995.

The IDE staff will provide the divisions with a list of all IDE applications which must be categorized. This will include only those IDEs in the database which are approved. IDEs which have been terminated will be considered exempt from this IA agreement and thus will not be assigned to a reimbursement category. The IDE staff will also provide ODE's reviewing divisions with a standardized form to allow the information to be captured in a uniform fashion. IDE staff consultation and concurrence is required for any IDE application which is assigned to Category A (i.e., Experimental). (The boilerplate checklist (Document H-1 on the LAN) which identifies the rationale for this categorization determination must be signed-off by both division management and the IDE staff. Also see Attachment B)

In order to make this information publicly available, the Division of Small Manufacturers Assistance (DSMA) will post on its electronic docket a list of the approved IDEs (IDE numbers only) and the corresponding reimbursement category.

B. Phase II: IDEs Approved after September 15, 1995

On September 18, 1995, the divisions will become responsible for determining the reimbursement categorization for those IDEs which are approved, conditionally approved, or deemed approved (unless deemed approved and immediately withdrawn). As previously noted, it is anticipated that in most instances categorization will be possible on the basis of a quick review of the division's records and the IDE database. As discussed above, for those cases where an IDE is assigned to Category A, the branch chief must contact the IDE staff prior to issuing the approval letter or otherwise notifying the sponsor or HCFA of this categorization decision. The IDE staff will review the decision and notify the division of its concurrence.

IDE boilerplate approval letters ("full", conditional, and deemed approved) for original IDEs and amendments will be modified as follows:

1. The reference block will be modified to include not only the IDE number and the name of the device but also the proposed indication for use for the device as stated in the clinical protocol and the HCFA Reimbursement Category: A (or B).

2. HCFA will be added to the distribution list at the bottom of all such letters. The Document Mail Center (DMC) will be responsible for mailing copies of these approval

letters to HCFA.

3. An enclosure entitled, "Procedures to Request Re-evaluation of Categorization Decisions" must be included in the approval letters when a Category A determination is made.

In order to create a written record of the basis for each categorization decision, reviewers must complete the checklist provided by the IDE staff (See Attachment B or document H-1 on the LAN). By using this checklist, the criterion which served as the basis for the categorization decision of the investigational device will be included in the IDE file as the checklist must be attached to the last page of the review memo. The categorization determination (category and reason code) must also be recorded on the tracking sheets for all original IDEs and amendments which are approved. (If this information is not included on the tracking sheet, the DMC will not be able to log the IDE out of the tracking system.) The DMC will be responsible for entering this information into the IDE database when the IDE is logged out of the tracking system.

The Office of Systems and Management has modified the IDE database to capture the reimbursement category and reason code assigned to each approved IDE. Such modifications will permit both searching of the IDE database and the generation of reports based on this criteria.

C. Changes in IDE Status

In the event that the approval of an IDE application is withdrawn, it is imperative that HCFA be apprised of this fact as soon as possible. Therefore, if after consultation with the IDE staff, the decision is made to withdraw approval of the IDE application, the reviewing division will be responsible for FAXING a copy of the final order which withdraws approval of the IDE to HCFA at the same time that the sponsor is notified of the withdrawal of approval. (See IDE boilerplate letter G-30A for the name of the HCFA contact person and FAX number to which this information should be forwarded.) HCFA should <u>not</u> be notified of <u>proposed</u> withdrawal letters as these may not lead to the final order.

D. Confidentiality of Categorization Determination

As provided for under 21 CFR 812.38(a), all information pertaining to an IDE, regardless of its status, is confidential. This includes the categorization determination. Thus, except for the information which DSMA will post on its electronic docket, information regarding the reimbursement categorization decision should only be released to the sponsor of the IDE and to HCFA. Therefore, the divisions should refer inquiries (particularly those from physicians, patients, and insurance carriers) pertaining to the HCFA reimbursement policy to Sharon Hippler at: HCFA, 7500 Security Boulevard, C4-04-05, Baltimore, MD 21244 or (410) 786-4633.

E. Sponsor Inquiries and Requests for Re-evaluation of Categorization Decisions

The division may discuss the basis for the reimbursement categorization with the study sponsor. A request for re-evaluation of the reimbursement determination must be submitted in writing to FDA as an IDE supplement. Upon receipt of this request, the reviewing division will reconsider the original decision and issue a letter setting forth the basis of its final decision. The appropriate boilerplate letter should be used when responding to such requests, and IDE Staff concurrence must be obtained before the letter is issued. After this point, the sponsor must refer any subsequent inquiries regarding the categorization decision to HCFA as FDA's determination may be only one of several factors considered when the reimbursement decision is made and HCFA is the final arbiter of all reimbursement decisions.

F. Updating of the Categorization Decisions

If the circumstances which led to the original categorization determination change (e.g., a PMA is approved for a device similar to one under investigation), the reviewing division will be responsible for reconsidering the categorization designation for all IDEs which may have been affected by this change. Any resulting modifications must be immediately reported to the IDE Staff. The IDE Staff will be responsible for reporting these changes in the categorization designation to both HCFA and the sponsor of the IDE.

Attachment A
Interagency Agreement

Between the Health Care Financing Administration (HCFA) and the Food and Drug Administration (FDA) regarding Medicare coverage of certain investigational medical devices.

I. Purpose

To establish a process by which FDA will assist HCFA to place IDE devices into categories based on the level of risk the device presents to patients. This categorization will be used by HCFA as part of its determination of which devices meet the requirements for Medicare coverage under section 1862(a)(1)(A) of the Social Security Act (the, "reasonable and necessary" clause). To be covered under Medicare, the device must be reasonable and necessary for the diagnosis or treatment of an illness or injury, or to improve the functioning of a malformed body member.

II. Authority

The legal authority to enter into this Agreement is provided in sections 1874 and

1862(a)(1)(A) of the Social Security Act and sections 520(g) and 701(a) of the Federal Food, Drug and Cosmetic Act.

III. Background

In his National Performance Review, Vice President Gore directed the health agencies of the Department of Health and Human Services (HHS) to review their policies and processes to determine which requirements could be reduced or eliminated without lowering health and safety standards. In accordance with this directive, FDA reviewed its current regulatory approval processes and HCFA reviewed its Medicare coverage policies for medical devices that have not received full FDA approval.

The Medicare program has historically interpreted the statutory terms "reasonable and necessary" to mean that a service or medical device must be safe and effective, medically necessary and appropriate, and not experimental in order to qualify for reimbursement. For Medicare coverage purposes, the term experimental has been used synonymously with the term investigational. Therefore, an approved Investigational Device Exemption (IDE) application served as an indication that the device was not "reasonable and necessary" within the meaning of the Medicare program. Under this policy, Medicare coverage was denied for devices that require, but have yet to receive, 510(k) clearance and those that have received an IDE but have not received Premarket Approval (PMA).

There is increasing recognition that there are devices which are refinements of existing technologies or replications of existing technologies by other manufacturers. Many of these devices are placed within the IDE category as a means of gathering the scientific information necessary for FDA to establish the safety and effectiveness of the particular device, even though there is scientific evidence that the type of device can be safe and effective. Arguably, these devices could be viewed as "reasonable and necessary" by Medicare and recognized for payment if it were possible to identify them in the FDA's process.

Accordingly, FDA and HCFA are developing a revised policy to meet the needs of Medicare beneficiaries. The purpose of this effort is to determine if it is feasible to expand. Medicare coverage to include certain medical devices that have not yet received FDA marketing approval/clearance without compromising the safety of medical care provided to Medicare beneficiaries. The intent is to devise ways to:

- assure Medicare beneficiaries greater access to advances in proven medical technology;
- encourage clinical researchers to conduct high quality studies; and,
- clarify Medicare coverage of reasonable and necessary medical services during clinical trials for investigational devices.

IV. Scope of Work and Responsibilities

The Health Care Financing Administration, in conjunction with the Food and Drug Administration, will develop a process to differentiate between novel, first-of-a-kind medical devices and newer generations of proven technologies. New Medicare policies will be established in accordance with the requirements for Federal rule-making under section 553 of the Administrative Procedure Act.

This Interagency Agreement (IA) supports this process under which HCFA will establish a stratified policy for Medicare coverage of certain IDE devices under FDA review. For purposes of assisting HCFA in determining Medicare coverage, the FDA will place all IDEs it approves in one of two categories:

- Category A - Experimental- innovative devices believed to be in class III for which "absolute risk" of the device type has not been established (i.e., initial questions of safety and effectiveness have not been resolved). That is, FDA is unsure whether the device type can be safe and effective.

- Category B - Non-experimental/Investigational - device types believed to be in classes I or II or device types believed to be in class III where the incremental risk is the primary risk in question (i.e., underlying questions of safety and effectiveness of that device type have been resolved), or it is known that the device type can be safe and effective because, for example, other manufacturers have obtained FDA approval for that device type.[1]

In order to properly categorize device investigations, HCFA and FDA have agreed to employ criteria outlined in the Attachment. As experience is gained in making categorizations, the criteria may be updated.

For purposes of determining Medicare coverage, medical devices classified under this system as "Category B: Nonexperimental/Investigational," could be viewed as "reasonable and necessary" if they also meet all other Medicare coverage requirements. In some cases, HCFA may also wish to conduct a separate assessment of the device to determine medical necessity

[1] Note: Under the Food, Drug, and Cosmetic Act, devices are categorized into three classes. Class I devices are the least regulated devices. These are devices that FDA has determined need to be subject only to general controls, such as good manufacturing practice regulations. Class II devices are those which, in addition to general controls, require special controls, such as performance standards or post-market surveillance, to assure safety and effectiveness. Class III devices are - those which cannot be classified into Class I or Class II because insufficient information exists to determine that either special or general controls would provide reasonable assurance of safety and effectiveness. Class III devices require Pre-Market Approval (PMA).

and appropriateness specifically with respect to Medicare beneficiaries.

In support of this basic agreement HCFA and FDA agree to the following:

- FDA will assign each FDA-approved IDE to one of the two categories listed in the Attachment and notify HCFA of its categorization no less than each calendar quarter, either by electronic means or written communication.

- Medicare coverage of devices under "investigation" is predicated, in part, upon their status with FDA. In the event a sponsor loses its category B categorization or violates relevant IDE requirements necessitating FDA's withdrawal of approval of the IDE, FDA will immediately notify HCFA in order that HCFA may reevaluate the coverage status of the device under Medicare. HCFA will establish specific procedures for the withdrawal of Medicare coverage. These procedures will be described in Medicare regulations.

- FDA-approved IDE study protocols for each clinical study will require that devices be available in a circumscribed number of sites for an approved number of patients. HCFA will provide Medicare coverage and payments in accordance with these limitations and other" protocol requirements (i.e., services provided by certain health care practitioners).

- FDA will assign each IDE an identification code or number which will enable HCFA to establish special claims processing procedures for Medicare claims associated with the clinical trial. FDA will complete this process for existing IDEs by November 1, 1995.

- FDA will require that the sponsor/manufacturer and clinical-investigators adhere to, pertinent regulations, including obtaining informed consent for all patients participating in the clinical trial.

- FDA will establish a process for the reconsideration of the categorization of IDE devices. As part of this process, FDA will analyze all information submitted by a party in support of a request for reconsideration. HCFA will establish a process to review requests for reconsideration that are denied by FDA. FDA will provide necessary technical and expert support relating to FDA's categorization of devices to HCFA during the review process. FDA will provide information to HCFA to substantiate its decision on the categorization of each medical device under review.

- Reimbursement under the Medicare program for a device under an approved IDE will be limited to what Medicare would have paid for a comparable approved device.

V. Period of Agreement

This agreement takes effect upon the signatures of the two parties. The policy will be effective when final regulations are published in the Federal Register, expected to be on or about November 1, 1995. The agreement will continue in effect for an indefinite period.

VI. Modification/Cancellation Provisions

This Interagency Agreement (IA) may be modified at any time by mutual agreement of the patties. It may be canceled if both parties so agree in connection with a review, or if a Federal statute is enacted that materially affects the IA. In the event there is a cancellation of the IA, that cancellation will not be effective for at least 6 months.

VII. Confidentiality of IDE Information

FDA will provide HCFA access to all information in the IDE application for making Medicare coverage and payment determinations, insuring protection against program fraud and abuse, and claims processing. All IDE applications will remain on FDA premises. However, relevant portions of these applications may be duplicated by HCFA, as necessary, for purposes of Medicare coverage determinations.

To the extent that such information is in the possession and control of HCFA, it is subject to the disclosure and withholding rules established by Federal statutes and regulations. Applicable Federal statutes include, but are not limited to, the Freedom of Information Act (5 U.S.C. 552), the Privacy Act (5 U.S.C. 552a), the Social Security Act (42 U.S.C. 1306a), and the Trade Secrets Act (18 U.S.C 1905). Under this agreement, FDA will have a role in ensuring that its data release standards are met, either by reviewing any materials and paperwork to be released by HCFA, or through some other forms of oversight. Moreover, HCFA has no present intention of disclosing, or authorizing the disclosure of, individual/patient or proprietary information.

Attachment B
Criteria for Categorization of Investigational Devices

Category A: Experimental

1. Class III devices of a type for which no marketing application has been approved through the

Premarket approval (PMA) process for any indication for use. (For preamendments Class III devices, refer to the criteria under Category B); or

2. Class III devices that would otherwise be in Category B but have undergone significant modification for a new indication or use.

Category B: Non-experimental/Investigational

1. Devices, regardless of the classification, under investigation to establish substantial equivalence to a predicate device, i.e., to establish substantial equivalence to a previously/currently legally marketed device: or

2. Class III devices whose technological characteristics and indications for use are comparable to a legally marketed device; or

3. Class III devices with technological advances compared to a legally marketed device, i.e., a device with technological changes that represent advances to a device that has already received pre-market approval (generational changes); or

4. Class III devices that are comparable to a legally marketed device but are under investigation for a new indication for use. For purposes of studying the new indication, no significant modifications to the device were required; or

5. Pre-amendments Class III devices that become the subject of an IDE after FDA requires Premarket approval, i.e., no PMA was submitted or the PMA was denied; or

6. Non-significant risk device investigations for which FDA required the submission of an IDE.

Note: Some investigational devices may exhibit unique characteristics or raise safety concerns that make additional consideration necessary. For these devices, HCFA and FDA will agree on the additional criteria to be used. FDA will then use this criteria to assign the device(s) to a category. As experience is gained in the categorization process, this attachment may be modified.

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FEASIBILITY STUDIES (5/17/89) IDE MEMORANDUM #D89-1

Introduction

It is relatively easy for a sponsor to identify a feasibility study by merely pointing out that the

study involves a new device or a new technology and will involve only a few human subjects. It is much more difficult to establish the criteria for relief from specific requirements of the IDE regulation while assuring that patients are not placed at unreasonable risk. Relief can only be granted on a case-by-case basis, and continual assessment and analysis of the review of feasibility studies are essential to developing more concise guidance. This guidance outlines principles which should be considered when reviewing IDE applications for feasibility studies. It is expected that application of these principles will facilitate the review and approval of feasibility studies to the extent consistent with the safety and welfare of the research subjects and within ethical standards.

The Concept of Feasibility Studies

In a developmental process, a device is designed to meet a clinical need and testing begins in the laboratory using animal or bench methodology. Once the design and operating parameters have been subject to adequate preclinical tests, the developer may wish to conduct an initial limited study in humans to confirm the design and operating specifications before beginning an extensive clinical trial. The initial study may indicate that major or minor changes in the device or its manufacture are necessary before proceeding. It may also indicate that the device does not meet expectations and the study should be terminated. The performance of a device in a limited study serves to establish the parameters such as sample size and indices of measurement for a larger clinical study. Inherent in the utility of a limited study is the importance of maintaining sufficient flexibility for a researcher to make adjustments in the device, its manufacture, or the investigational plan in the early stages of clinical testing without the need for repeated prior approval from FDA.

Applicability

This guidance applies to limited clinical investigations of significant risk medical devices which are intended to provide data on the device's feasibility for diagnostic or therapeutic clinical use. IDE applications subject to the guidance are those which are identified by the sponsor as feasibility studies and which demonstrate that they meet the general considerations applicable to such studies. A feasibility study may also be identified as a phase 1 study, a pilot study, a prototype study, or an introductory trial.

Interactions with Sponsors

FDA encourages early and continued interactions with device innovators and potential IDE sponsors to establish a rapport which will expedite the review process. Device technology is advancing rapidly and FDA must develop and nurture lines of communication in order to anticipate problems, training needs, and other resources necessary to review applications. The sponsor or researcher gains by being able to plan an acceptable preclinical and clinical approach to product development.

General Considerations for Original and Supplemental IDEs

Original IDEs. IDE applications for feasibility studies will vary in scope but typically will include one investigator at one site with a limited number of subjects, usually ten or less. Data from the feasibility study will not be considered as pivotal evidence of safety and effectiveness but rather as a basis to finalize and confirm the device design and determine its potential for further development. FDA will continue to require that an IDE application for a feasibility study address all the elements of an IDE application as stated in the regulations, unless a waiver is approved.

Generally, reviewers will focus their attention on identification of safety issues (e.g., serious flaws in device design and testing) which are critical to the protection of the health, safety, and welfare of subjects. Additional concerns may be delayed until the next phase of development, i.e., the extended safety and effectiveness study. The IDE regulation provides that an application may include anticipated changes to a device during the course of an investigation. For a feasibility study, FDA and the sponsor may employ this provision to qualify a range of device changes and testing parameters that can be undertaken by the sponsor without the need for further FDA approval.

Supplemental IDEs. The IDE regulation provides that changes affecting the scientific soundness or the rights, safety, and welfare of subjects need to be submitted to FDA for approval prior to implementation. IRB approval is also required when the changes affect the rights, safety, and welfare of subjects. FDA and sponsors should use these criteria to the maximum extent possible to limit the type of changes needed to be submitted as supplements. It is the sponsor's responsibility to determine whether a change meets the criteria. All changes, whether major, minor, or submitted as a supplement, should be described in the progress reports, end-of-study reports, and in requests for expansion of the investigation.

Specific IDE Requirements and Considerations

An IDE application for a feasibility study must address all the elements required by the IDE regulation unless a waiver is granted for a specific element. Elements that are not relevant may be indicated as "not applicable." Summary information, in lieu of full reports, is acceptable provided that the summary is sufficiently detailed and comprehensive to permit knowledgeable evaluation of the data.

Preclinical studies. It is the sponsor's responsibility to define and conduct adequate tests to establish the lack of unreasonable risk and the expected performance of a device prior to clinical use. A limited trial may represent the initial introduction of a device into a human population; therefore, FDA must be assured that a sufficient battery of tests has been completed. It is the prerogative of the sponsor to indicate whether some preclinical tests (e.g., chronic toxicity) are

not essential to early clinical studies and will be initiated only if the device will undergo further clinical study.

Investigational plan. The sponsor must include a thorough risk analysis which describes the risks to the subject, how they will be minimized, and a justification that they are reasonable in relation to the expected benefits. The scope and duration of limited studies will vary, but in general, are less ambitious than full clinical studies which provide the pivotal evidence of safety and effectiveness. The investigational plan should have a valid scientific objective and reasonable study protocol. Disapprovals should be limited to situations where there are critical safety-related concerns. Other deficiencies can be corrected or clarified under a conditional approval decision.

Manufacturing and control data. In some developmental programs which lead to feasibility studies, FDA recognizes that traditional manufacturing information may not exist. Often a device does not proceed to further development if the early studies do not prove satisfactory; therefore, only pilot manufacturing processes may be used. It is incumbent upon the sponsor to establish a reasonable process of design, manufacture, quality control, and testing and to indicate to FDA in an IDE application when other standard procedures are unnecessary or premature. FDA reviewers should tailor their deficiencies to the circumstances that exist and the stage of development. Expanded clinical studies may require additional assurances regarding manufacture and quality control as the number of devices to be distributed increases. The conditional approval decision should be employed as much as possible.

Informed Consent. Attention should be paid to the informed consent s description of the nature of the study, i.e., explanation of the purpose of the research, and indication that the subject is one of the first exposed to the device.

Other IDE application requirements. All other aspects of IDE applications for feasibility studies including investigator information and agreement, IRB information, sales information, environmental impact statements, and labeling should be evaluated under a conditional approval decision unless there are extenuating circumstances.

Analysis of Feasibility Studies

ODE will conduct an analysis of the types of IDE applications being submitted for feasibility studies. The purpose of this analysis is to determine whether the guidance is providing sufficient direction to reviewers and flexibility to researchers. It will also further establish the nature and extent of feasibility studies. The IDE Staff will collect the following information in their analysis: device type, objectives of the study, study design, number of investigators and sites, size of study sample, duration of study, conclusions of the study, use of the data, and percent of device types to expanded trials.

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BIOLOGICAL EVALUATION OF MEDICAL DEVICES: USE OF ISO-10993 (5/1/95)
GENERAL PROGRAM MEMORANDUM - #G95-1

Purpose

The purpose of this memo is to replace, after July 1, 1995, the use of ODE General Program Memorandum G87-1, entitled "Tripartite Biocompatibility Guidance", dated April 24, 1987 with Part-1 of the ISO standard "Biological Evaluation of Medical Devices", which includes an FDA-modified matrix.

Background

Biological evaluation of medical devices is performed to determine the potential toxicity resulting from contact of the component materials of the device with the body. The device materials should not, either directly or through the release of their material constituents:
(i) produce adverse local or systemic effects; (ii) be carcinogenic; or, (iii) produce adverse reproductive and developmental effects. Therefore, evaluation of any new device intended for human use requires data from systematic testing to ensure that the benefits provided by the final product will exceed any potential risks produced by device materials.

When selecting the appropriate tests for biological evaluation of a medical device, one must consider the chemical characteristics of device materials and the nature, degree, frequency and duration of its exposure to the body. In general, the tests include: acute, sub-chronic and chronic toxicity; irritation to skin, eyes and mucosal surfaces; sensitization; hemocompatibility; genotoxicity; carcinogenicity; and, effects on reproduction including developmental effects. However, depending on varying characteristics and intended uses of devices as well as the nature of contact, these general tests may not be sufficient to demonstrate the safety of some specialized devices. Additional tests for specific target organ toxicity, such as neurotoxicity and immunotoxicity may be necessary for some devices. For example, a neurological device with direct contact with brain parenchyma and cerebrospinal fluid (CSF) may require an animal implant test to evaluate its effects on the brain parenchyma, susceptibility to seizure, and effects on the functional mechanism of choroid plexus and arachnoid villi to secrete and absorb (CSF). The specific clinical application and the materials used in the manufacture of the new device determines which tests are appropriate.

Some devices are made of materials that have been well characterized chemically and physically in the published literature and have a long history of safe use. For the purposes of demonstrating the substantial equivalence of such devices to other marketed products, it may not be necessary to conduct all the tests suggested in the FDA matrix of this guidance. FDA reviewers are advised to use their scientific judgement in determining which tests are required for the demonstration of

substantial equivalence under section 510(k). In such situations, the manufacturer must document the use of a particular material in a legally marketed predicate device or a legally marketed device with comparable patient exposure.

International Guidance and Standards

In 1986, FDA, Health and Welfare Canada, and Health and Social Services UK issued the Tripartite Biocompatibility Guidance for Medical Devices. This Guidance has been used by FDA reviewers, as well as by manufacturers of medical devices, in selecting appropriate tests to evaluate the adverse biological responses to medical devices. Since that time, the International Standards Organization (ISO), in an effort to harmonize biocompatibility testing, developed a standard for biological evaluation of medical devices (ISO 10993). The scope of this 12-part standard is to evaluate the effects of medical device materials on the body. The first part of this standard "Biological Evaluation of Medical Devices: Part 1: Evaluation and Testing", provides guidance for selecting the tests to evaluate the biological response to medical devices. Most of the other parts of the ISO standard deal with appropriate methods to conduct the biological tests suggested in Part 1 of the standard.

ISO 10993, Part 1, and the FDA-modified Matrix

The ISO Standard, Part 1, uses an approach to test selection that is very similar to the currently-used Tripartite Guidance, including the same seven principles. It also uses a tabular format (matrix) for laying out the test requirements based on the various factors discussed above. The matrix consist of two tables. See Attachment A, Table 1 - Initial Evaluation Tests for Consideration, and Attachment B, Table 2 - Supplementary Evaluation Tests for Consideration. Attachment C is a biocompatibility flow chart for the selection of toxicity tests for 510(k)s. It may be applicable to some PMAs also but not all PMAs. In addition, FDA is in the process of preparing toxicology profiles for specific devices. These profiles will assist in determining appropriate toxicology tests for these devices.
To harmonize biological response testing with the requirements of other countries, FDA will apply the ISO standard, Part 1, in the review process in lieu of the Tripartite Biocompatibility Guidance.

FDA notes that the ISO standard acknowledges certain kinds of discrepancies. It states "due to diversity of medical devices, it is recognized that not all tests identified in a category will be necessary and practical for any given device. It is indispensable for testing that each device shall be considered on its own mertis: additional tests not indicated in the table may be necessary." In keeping with this inherent flexibility of the ISO standard, FDA has made several modifications to the testing required by ISO 10993-Part 1. These modifications are required for the category of surface devices permanently contacting mucosal membranes (e.g., IUDs). The ISO standard would not require acute, sub-chronic, chronic toxicity and implantation tests. Also, for externally

communicating devices, tissue/bone/dentin with prolonged and permanent contact (e.g., dental cements, filling materials etc.), the ISO standard does not require irritation, systemic toxicity, acute, sub-chronic and chronic toxicity tests. Therefore, FDA has included these types of tests in the matrix.

Although several tests were added to the matrix, reviewers should note that some tests are commonly requested while other tests are to be considered and only asked for on a case-by-case basis. Thus, the modified matrix is only a framework for the selection of tests and not a checklist of every required test. Reviewers should avoid proscriptive interpretation of the matrix. If a reviewer is uncertain about the applicability of a specific type of test for a specific device, the reviewer should consult toxicologists in ODE.

FDA expects that manufacturers will consider performing the additional tests for certain categories of devices suggested in the FDA-modified matrix. This does not mean that all the tests suggested in the modified matrix are essential and relevant for all devices. In addition, device manufacturers are advised to consider tests to detect chemical components of device materials which may be pyrogenic. We believe that ISO 10993, Part 1, and appropriate consideration of the additional tests suggested by knowledgeable individuals will generate adequate biological data to meet FDA's requirements. Reviewers in the Office of Device Evaluation will accept data developed according to the ISO-10993, Part 1, with the matrix as modified and presented in this memorandum (#G95-1).

Manufacturers are advised to initiate discussions with the appropriate review division in the Office of Device Evaluation, CDRH, prior to the initiation of expensive, long-term testing of any new device materials to ensure that the proper testing will be conducted. We also recognize that an ISO standard is a document that undergoes periodic review and is subject to revision. ODE will notify manufacturers of any future revisions to the ISO standard referenced here that affect this document's requirements and expectations.

Table 1 - Initial Evaluation Tests for Consideration.*

Device Categories			Biological Effect							
Body contact (see 4.1)		Contact duration (see 4.2) A-limited (<24 h) B-prolonged (24 h to 30 days) C-permanent (>30 days)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Sub-chronic toxicity (sub-acute toxicity)[1]	Genotoxicity	Implantation	Haemocompatibility
Surface devices	Skin	A	X	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X	O	O		O	
		C	X	X	X	O	X	X	O	
	Breached or compromised surfaces	A	X	X	X	O				
		B	X	X	X	O	O		O	
		C	X	X	X	O	X	X	O	
External communicating devices	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X	O			X
		C	X	X	O	X	X	X	O	X
	Tissue/bone/ dentin communicating[1]	A	X	X	X	O				
		B	X	X	O	O	O	X	X	
		C	X	X	O	O	O	X	X	
	Circulating blood	A	X	X	X	X		O[2]		X
		B	X	X	X	X	O	X	O	X
		C	X	X	X	X	X	X	O	X
Implant Devices	Tissue/ bone	A	X	X	X	O				
		B	X	X	O	O	O	X	X	
		C	X	X	O	O	O	X	X	
	Blood	A	X	X	X	X			X	X
		B	X	X	X	X	O	X	X	X
		C	X	X	X	X	X	X	X	X

X = ISO Evaluation Tests for Consideration
O = Additional Tests which may be applicable
Note [1] Tissue includes tissue fluids and subcutaneous spaces
Note [2] For all devices used in extracorporial circuits

*See Table 2 for Supplementary Evaluation Tests

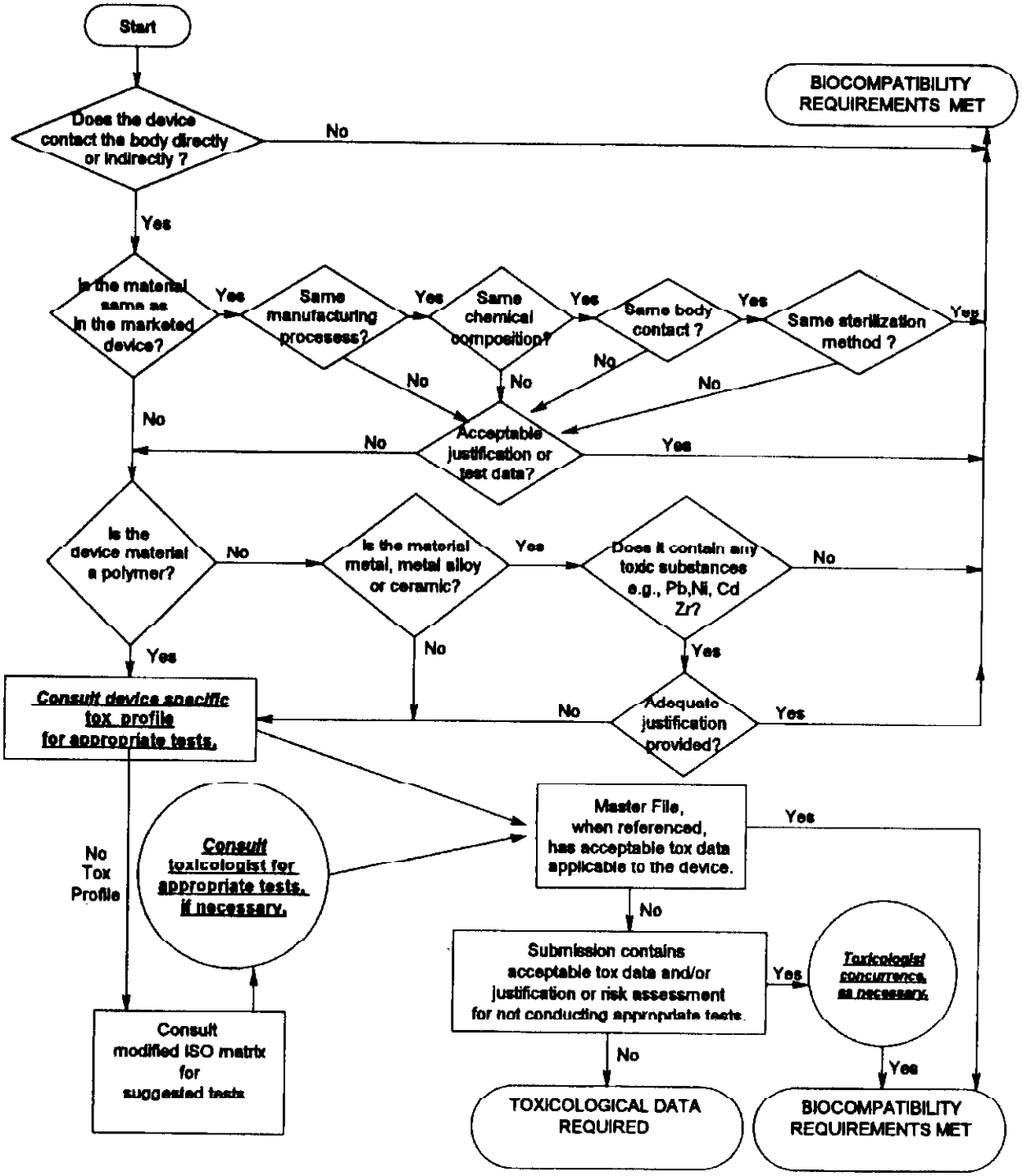
Table 2 - Supplementary Evaluation Tests for Consideration.*

Device Categories			Biological Effect			
Body contact (see 4.1)		Contact duration (see 4.2) A-limited (<24 h) B-prolonged (24 h to 30 days) C-permanent (>30 days)	Chronic toxicity	Carcinogenicity	Reproductive/Developmental	Biodegradation
Surface devices	Skin	A				
		B				
		C				
	Mucosal membrane	A				
		B				
		C	O			
	Breached or compromised surfaces	A				
		B				
		C	O			
External communicating devices	Blood path, indirect	A				
		B				
		C	X	X		
	Tissue/bone/dentin communicating	A				
		B				
		C	O	X		
	Circulating blood	A				
		B				
		C	X	X		
Implant Devices	Tissue/bone	A				
		B				
		C	X	X		
	Blood	A				
		B				
		C	X	X		

X = ISO Evaluation Tests for Consideration
O = Additional Tests which may be applicable

*See Table 1 for Initial Evaluation Tests.

Biocompatibility Flow Chart for the Selection of Toxicity Tests for 510(k)s



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PMA/510(K) EXPEDITED REVIEW (5/20/94) GENERAL PROGRAM MEMORANDUM #G94-2

Purpose

This document is intended to establish criteria and procedures under which expedited review would apply to Premarket Approval Applications (PMAs) and Premarket Notifications (510(k)s) for medical devices. This memorandum rescinds and replaces 510(k) memorandum #K86-1, "510(k) Expedited Review" and General Program memorandum #G89-2, "IDE/PMA Expedited Review Process."

Introduction

These procedures are based upon the Management Action Plan (MAP) initiative paper entitled "PMA/510(k) Expedited Review Process." This Blue Book Memorandum embodies the guidance procedures flowing from that issue paper and hereby implements the principles in that document as the policy of ODE. This Blue Book Memorandum will be used by ODE reviewers in applying these guidance procedures to the review of incoming PMAs and 510(k)s.

FDA believes it is in the interest of the public health to review PMAs and 510(k)s for certain medical devices in an expedited manner. Expedited review will generally be considered when a device offers a potential for clinically meaningful benefit as compared to the existing alternatives (preventative, diagnostic, or therapeutic) or when the new medical device promises to provide a revolutionary advance (not incremental advantage) over currently available alternative modalities.

Granting of expedited review status means that the marketing application would receive priority review before other pending PMAs and 510(k)s, i.e., the application will be placed at the beginning of the appropriate review queue. If multiple applications for the same type medical device offering comparable advantage over existing approved alternatives have been granted expedited review, they will be reviewed with priority according to their respective submission due dates. Once one of the applications is approved, those of the same type still pending will generally lose their expedited review status as regards review resources but retain their place in the review queue.

Except as specifically noted, documents under expedited review status would be subject to all other controls and requirements applicable to comparable documents in the standard review process. In this effort, it is imperative that valid scientific evidence, as required by Title 21 of the Code of Federal Regulations, be used to support an application subject to expedited review. This

evidence will generally be obtained from well designed, monitored, and controlled clinical trials, when appropriate, so that the true merit of the medical device may be evaluated as promptly and efficiently as possible.

Criteria

Expedited review will be considered for a device intended for or meeting at least one of the following criteria:

1. **Life-threatening or irreversibly debilitating conditions with no alternative modality**. The condition or potential condition/disease is serious or life-threatening or presents a risk of serious morbidity and no alternative legally marketed diagnostic/therapeutic modality exists. NOTE: Applications in this category granted expedited review status will not only be placed at the beginning of the review queue but will also undergo accelerated review as review staff are available to be assigned.

2. **Life-threatening or irreversibly debilitating conditions with approved alternatives extant**, but where new device provides for clinically important earlier diagnosis or significant advances in safety and/or effectiveness over existing alternatives.

3. **A revolutionary (breakthrough) device**. The medical device represents a clear clinically meaningful advantage over existing technology defined as having major (not incremental) increased effectiveness or reduced risk compared to existing technology. Devices which meet this criteria must have been evaluated utilizing well defined, clinically meaningful outcome measures or acceptable surrogates for such measures.

4. **A specific public health benefit.** The availability of the device is otherwise in the best interest of the public health. For example, a device designed or modified to address an unanticipated serious failure occurring in a critical component of an approved device for which there are no alternatives, or for which alternative treatment would entail substantial risk of morbidity for the patient.

Procedures

1. **Identification of applications for expedited review.** Each ODE reviewing Division will identify those applications which merit expedited review, either during the IDE stage, through pre- submission meetings with the applicant or through a preliminary evaluation of the submitted application. This evaluation will take into consideration the criteria set forth above (nature of the medical device, the target population, the alternative preventative, diagnostic or therapeutic modalities and the potential benefit of the device to the public health).

   Sponsors are encouraged to identify early in their correspondence with the Center devices

which they feel merit expedited review by the criteria listed above.

2. **Determination of expedited review.** The ODE Division Director will authorize the decision to expedite review within the following timeframes:

   510(k)s - The decision to expedite should be made within 30 days from the receipt date of the application.

   PMAs - The evaluation for expedited review will be part of the 45 day filing review.

3. **Documentation and processing.** After this determination has been made, the Division will prepare a written memo to the administrative record which highlights, using the criteria outlined above, the reasons why the marketing application has received expedited review status. A copy of this memo should be provided to the Director, ODE and the 510(k) or PMA Section of the Program Operations Staff. The Division will prepare and issue a letter, based upon the current boilerplate letter provided by the POS Staff, conveying to the applicant the expedited review status. The notification conveying expedited review status may be incorporated in filing letters. A copy of the letter must be forwarded to the POS office for inclusion in the official administrative file and for updating databases. A boilerplate will also be issued to the applicant if the 510(k) or PMA is later removed from expedited review status.

4. **Resource management.** It will be the responsibility of the Director of the reviewing Division to ensure that the application is reviewed in the most efficient manner, tracked as an expedited review, and completed within the statutory time frames. It is recognized that implementation of this policy will impact on all of the review work of the Division. Additional resources may be necessary for review of the marketing applications granted expedited review. All of the following resource issues should be considered to accommodate the expedited review process:

   a) a shift in the workload within the affected reviewing Division may be necessary;

   b) scientists from other Divisions or from outside of ODE may be called upon to provide support to those areas in ODE where the standard review queue would otherwise be affected by the needed redistributions of the workload; and

   c) review of the other non-expedited applications in that reviewing Division may be delayed.

5. **Monitoring.** The Office of the Director, ODE, will periodically review, approximately every 90 days, decisions to expedite review to provide feedback to the Division Directors regarding

consistency of decision making within and among Divisions.

In a separate memo to the Director, ODE, for each application that will receive expedited review, the Division should:

a) discuss the level of concerted effort the application will require, i.e., a list of the types of reviewers necessary (medical officers, biologists, engineers, etc.) and the level of participation these reviewers will have in the review of the application;

b) designate who will be the lead reviewer; and

c) identify the displaced workload, e.g., briefly describe the lead reviewer(s) current workload and the applications that will have to be redistributed.

6. **Public disclosure.** The fact that an application has been reviewed under these expedited procedures will be first disclosed to the public only at the time of PMA approval or 510(k) clearance.

   A publicly disclosable paragraph should be provided to appropriate media outlets and FDA information sources (OST computer bulletin board, DSMA, etc.) so that interested outside parties may determine what types of applications have been granted expedited review.

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SPONSOR S RESPONSIBILITIES FOR SIGNIFICANT RISK DEVICE INVESTIGATIONS

This document is intended to assist sponsors in identifying and complying with their responsibilities in connection with the conduct of clinical investigations of medical devices that are deemed "significant risk" by the reviewing IRB or by FDA. For a complete description of their responsibilities, sponsors should refer to the actual text of the regulations cited below. In addition, sponsors should be aware that a clinical investigation must be conducted in accordance with any requirements imposed by the reviewing IRB, by institutional policies, or by state law.

General Duties (21 CFR 812.40):

1. Submitting the IDE application to FDA

2. Obtaining both FDA and IRB approvals for the investigation and submitting certification of IRB approval to FDA before shipping the device to any investigator
3. Obtaining FDA approval and IRB approval for a supplemental application before beginning that portion of the investigation
4. Selecting qualified investigators
5. Ensuring proper monitoring
6. Ensuring patient informed consent is obtained

Selection of Investigators (21 CFR 812.43):

1. Assuring selection of investigators qualified by training and experience
2. Shipping the investigational device only to participating investigators
3. Obtaining a signed investigator's agreement containing:
   a. investigator's curriculum vitae
   b. statement of investigator's relevant experience, including dates, location, extent, and type of experience
   c. if an investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to the termination
   d. statement of the investigator's commitment to:
      (1) conduct the investigation in accordance with the agreement, the investigational plan, Parts 50, 56, and 812, and any conditions of approval imposed by the IRB or FDA
      (2) supervise all testing of the device involving human subjects
      (3) ensure that the requirements for informed consent are met (21 CFR Part 50)
4. Providing investigators with the necessary information to conduct the investigation including, but not necessarily limited to:
   a. the investigational plan
   b. the report of prior investigations

Monitoring (21 CFR 812.46)

1. Selecting monitor(s) qualified by training and experience to monitor the progress of the investigation;

2. Securing compliance of all investigators in accordance with the signed investigator's agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any condition of approval imposed by the reviewing IRB or FDA. If compliance cannot be secured, shipment of the device to the investigator and the investigator's participation in the investigation must be discontinued;

3. Ensuring that significant new information about the investigation is provided to all reviewing IRBs, FDA, and investigators;

4. Evaluating all unanticipated adverse device effects and terminating the investigation, or portions of it, if that effect presents an unreasonable risk to subjects (reporting requirements are listed below.)

5. Resuming terminated investigations only after both FDA and IRB approvals are obtained.

Controlling Distribution and Disposition of Devices

Although investigators are responsible for ensuring that investigational devices are made available only to persons who are legally authorized to receive them (*see* 21 CFR 812.110(c)), sponsors also bear responsibility for taking proper measures to ensure that devices are not diverted outside of legally authorized channels. Sponsors may ship investigational devices only to qualified investigators participating in the clinical investigation (812.43(b)). Sponsors must also maintain complete, current, and accurate records pertaining to the shipment and disposition of the investigational device (812.140(b)). Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

To further ensure compliance with these requirements, sponsors should take appropriate measures to instruct investigators regarding their responsibilities with respect to recordkeeping and device disposition. The specific recordkeeping requirements for investigators are set forth at 812.140(a). Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (812.110(c)).

Prohibition of Promotion and Other Practices (21 CFR 812.7)

The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and investigators (or any person acting on behalf of a sponsor or investigator), and encompasses the following activities:

1. Promotion or test marketing of the investigational device;

2. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling;

3. Prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective; and,

4. Representing that the device is safe or effective for the purposes for which it is being investigated.

Supplemental Applications [21 CFR 812.35(a) and (b)]

Supplemental applications are required to be submitted to, and approved by, FDA in the following situations:

1. *Changes in the investigational plan*: FDA approval is required for any change that may affect the scientific soundness of the investigation or the rights, safety or welfare of the subjects. IRB approval is also required for changes that may affect the rights, safety or welfare of the subjects. The change in the investigational plan may not be implemented until FDA approval (and IRB approval, if required) is obtained.

2. *Addition of new institutions*: IRB approval is also required for new institutions. The investigation at the new institution(s) may not begin until both FDA and IRB approval(s) are obtained, and certification of IRB approval is submitted to FDA.

Maintaining Records [21 CFR 812.140(b)]

A sponsor shall maintain the following accurate, complete, and current records relating to an investigation (also *See* Table I, next page):

1. Correspondence (including reports) with another sponsor, monitor, investigators, an IRB or FDA

2. Records of shipment, including:
   a. name and address of consignee
   b. type and quantity of device

c. date of shipment
d. batch numbers or code marks

3. Records of disposition, describing:

   a. Batch number or code mark of devices returned, repaired, or disposed of by the investigator or other persons
   b. Reasons for and method of disposal

4. Signed investigator agreements

5. Adverse device effects (whether anticipated or unanticipated) and complaints

6. Any other records that FDA requires by regulation or by specific requirement for a category of investigation or a particular investigation

TABLE I
RESPONSIBILITIES FOR MAINTAINING RECORDS
FOR A SIGNIFICANT RISK DEVICE STUDY

Records	Maintained by Investigator	Maintained by Sponsor
All Correspondence Pertaining to the Investigation	✓	✓
Shipment, Receipt, Disposition	✓	✓
Device Administration and Use	✓	-
Subject Case Histories	✓	-
Informed Consent	✓	-
Protocols and Reasons for Deviations from Protocol	✓	-
Adverse Device Effects and Complaints	✓	✓
Signed Investigator Agreements	-	✓
Membership/Employment/Conflicts of Interest	-	✓
Minutes of Meetings	-	-

Submitting Reports [21 CFR 812.150(b)]:

A sponsor shall prepare and submit the following complete, accurate, and timely reports (also see Table II).

1. Unanticipated adverse device effects (with evaluation) to FDA, all IRBs, and investigators within 10 working days after notification by the investigator. Subsequent reports on the effect may be required by FDA.
2. Withdrawal of IRB approval
3. Withdrawal of FDA approval

4. Current 6-month investigator list
5. Annual progress report - see format for IDE progress report
6. Recall and device disposition (within 30 working days after the request was made)
7. Final report - see format for progress reports
8. Use of device without obtaining patient informed consent
9. Significant risk determinations by the IRB when proposed to be nonsignificant risk
10. Other reports requested by the IRB or FDA

TABLE II
RESPONSIBILITIES FOR PREPARING AND SUBMITTING REPORTS
FOR SIGNIFICANT RISK DEVICE STUDIES

Type of Report	Prepared by Investigators for	Prepared by Sponsors for
Unanticipated Adverse Effect Evaluation	Sponsors and IRBs	FDA, IRBs and Investigators
Withdrawal of IDE Approval	Sponsors	FDA, IRBs, and Investigators
Progress Report	Sponsors, Monitors and IRBs	FDA and IRBs
Final Report	Sponsors and IRBs	FDA, IRBs, and Investigators
Emergencies (Protocol Deviations)	Sponsors and IRBs	FDA
Inability to Obtain Informed Consent	Sponsors and IRBs	FDA
Withdrawal of FDA Approval	N/A	IRBs and Investigators
Current Investigator List	N/A	FDA
Recall and Device Disposition	N/A	FDA and IRBs
Records Maintenance Transfer	FDA	FDA
Significant Risk Determinations	N/A	FDA

Inspections [21 CFR 812.145]

Sponsors are required to permit FDA to enter and inspect (at reasonable times and in a reasonable manner) any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records or results from use of devices are kept). FDA may also inspect and copy all records relating to an investigation including, in certain situations, records which identify subjects.

INVESTIGATORS' RESPONSIBILITIES
FOR SIGNIFICANT RISK DEVICE INVESTIGATIONS

This document is intended to assist investigators in identifying and complying with their responsibilities in connection with the conduct of clinical investigations involving medical devices. Although this guidance primarily addresses duties imposed upon clinical investigators by regulations of the Food and Drug Administration (FDA), investigators should be cognizant of additional responsibilities that may derive from other sources (such as the study protocol itself, the investigator agreement, any conditions of approval imposed by FDA or the governing Institutional Review Board, as well as institutional policy and state law).

General Responsibilities of Investigators (21 CFR 812.100)

1. Ensuring that the investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations.

2. Protecting the rights, safety, and welfare of subjects under the investigator's care.

3. Controlling devices under investigation.

4. Ensuring that informed consent is obtained from each subject in accordance with 21 CFR Part 50, and that the study is not commenced until FDA and IRB approvals have been obtained.

Specific Responsibilities of Investigators (21 CFR 812.110)

1. Awaiting IRB approval and any necessary FDA approval before requesting written informed consent or permitting subject participation.

2. Conducting the investigation in accordance with:
   a. the signed agreement with the sponsor;
   b. the investigational plan;
   c. the regulations set forth in 21 CFR Part 812 and all other applicable FDA regulations; and
   d. any conditions of approval imposed by an IRB or FDA.

3. Supervising the use of the investigational device. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under 21 CFR Part 812 to receive it.

4. Disposing of the device properly. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

Maintaining Records (21 CFR 812.140)

An investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

1. Correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA.

2. Records of receipt, use or disposition of a device that relate to:
   a. the type and quantity of the device, dates of receipt, and batch numbers or code marks;
   b. names of all persons who received, used, or disposed of each device;
   c. the number of units of the device returned to the sponsor, repaired, or otherwise disposed of, and the reason(s) therefore.

3. Records of each subject's case history and exposure to the device, including:
   a. documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent;
   b. all relevant observations, including records concerning adverse device effects (whether anticipated or not), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests;
   c. a record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

4. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

5. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

Inspections (21 CFR 812.145)

Investigators are required to permit FDA to inspect and copy any records pertaining to the

investigation including, in certain situations, those which identify subjects.

Submitting Reports (21 CFR 812.150)

An investigator shall prepare and submit the following complete, accurate, and timely reports:

1. To the sponsor and the IRB:

   -Any *unanticipated adverse device effect* occurring during an investigation. (Due no later than 10 working days after the investigator first learns of the effect.)

   -*Progress reports* on the investigation. (These reports must be provided at regular intervals, but in no event less often than yearly. If there is a study monitor, a copy of the report should also be sent to the monitor.)

   -Any *deviation from the investigational plan* made to protect the life or physical well-being of a subject in an emergency. (Report is due as soon as possible but no later than 5 working days after the emergency occurs. Except in emergency situations, a protocol deviation requires prior sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA and IRB approval are required.)

   -Any use of the device *without obtaining informed consent*. (Due within 5 working days after such use.)

   -A *final report.* (Due within 3 months following termination or completion of the investigation or the investigator's part of the investigation. For additional guidance, see the discussion under the section entitled "Annual Progress Reports and Final Reports.")

   -*Any further information* requested by FDA or the IRB about any aspect of the investigation.

2. To the Sponsor:

   -*Withdrawal of IRB approval* of the investigator's part of an investigation. (Due within 5 working days of such action).

Investigational Device Distribution and Tracking

The IDE regulations prohibit an investigator from providing an investigational device to any person not authorized to receive it [21 CFR 812.110(c)]. The best strategy for reducing the risk that an investigational device could be improperly dispensed (whether purposely or inadvertently) is for the sponsor and the investigators to closely monitor the shipping, use, and final disposal of the device(s). Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor

directs [21 CFR 812.110(c)]. Investigators must also maintain complete, current and accurate records of the receipt, use, or disposition of investigational devices [21 CFR 812.140(a)(2)]. Specific recordkeeping requirements are set forth at 21 CFR 812.140(a).

Prohibition of Promotion and Other Practices (21 CFR 812.7)

The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and investigators (or any person acting on behalf of a sponsor or investigator), and encompasses the following activities:

1. Promotion or test marketing of the investigational device;

2. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling;

3. Prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective; and,

4. Representing that the device is safe or effective for the purposes for which it is being investigated.

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MONITORING OF CLINICAL INVESTIGATIONS (FEBRUARY 17, 1988)

This guidance reflects principles recognized by the scientific community as desirable approaches to monitoring clinical research involving human and animal subjects. These principles are not legal requirements but represent a standard of practice that is acceptable to FDA. A sponsor may rely upon this guidance or may develop different procedures. A sponsor who selects different procedures for monitoring a clinical investigation may, but is not required to, submit those procedures to FDA for review and comment to avoid the possibility of employing monitoring procedures that FDA might later determine to be inadequate. Sponsors wishing to obtain such a review should contact FDA's Bioresearch Program Coordinator (HFC-230), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Selection of a Monitor

A sponsor may designate one or more appropriately trained and qualified individuals to

monitor the progress of a clinical investigation. Physicians, veterinarians, clinical research associates, paramedical personnel, nurses, and engineers may be acceptable monitors depending on the type of product involved in the study. A monitor need not be a person qualified to diagnose and treat the disease or other condition for which the test article is under investigation, but somewhere in the direct line of review of the study data there should be a person so qualified.

For any given study, the factors that should be considered in determining the number of monitors and the education, training, or expertise necessary should include the:

number of investigators conducting the study;

number and location of the facilities in which the study is being conducted;

type of product involved in the study (i.e., drug for human use, drug for animal use, or a medical device);

complexity of the study; and

nature of the disease or other condition under study.

Written Monitoring Procedures

A sponsor should establish written procedures for monitoring clinical investigations to assure the quality of the study and to assure that each person involved in the monitoring process carries out his or her duties. A single written monitoring procedure need not be developed for each clinical investigation. Rather, a standardized written procedure, sufficiently detailed to cover the general aspects of clinical investigations, may be used as a basic monitoring plan and supplemented by more specific or additional monitoring procedures tailored to the individual clinical investigations.

Pre-Investigation Visits

A sponsor is responsible for assuring, through personal contact between the monitor and each investigator, that the investigator clearly understands and accepts the obligations incurred in undertaking a clinical investigation.

Prior to the initiation of a clinical investigation, the monitor should visit the site of the clinical investigation to assure that the investigator:

understands the investigational status of the test article and the requirements for its accountability;

understands the nature of the protocol or investigational plan;

understands the requirements for an adequate and well-controlled study;

understands and accepts the obligation to conduct the clinical investigation in accordance with Parts 812, 813, or any other applicable regulation;

understands and accepts the obligation to obtain informed consent in accordance with Part 56. The monitor should review a specimen of each consent document to be used by the investigator to assure that reasonably foreseeable risks are adequately explained;

understands and accepts the obligation to obtain IRB review and approval of a clinical investigation before the investigation may be initiated and to ensure a continuing review of the study by the IRB in accordance with Part 56 and to keep the sponsor informed of such IRB approval and subsequent IRB actions concerning the study;

has access to an adequate number of suitable subjects to conduct the investigation;

has adequate facilities for conducting the clinical investigation; and

has sufficient time from other obligations to carry out the responsibilities to which the investigator is committed by applicable regulations.

Periodic Visits

A sponsor is responsible for assuring throughout the clinical investigation that the investigator's obligations, as set forth in applicable regulations, are being fulfilled and that the facilities used in the clinical investigation continue to be acceptable. The most effective way to achieve this assurance is to maintain personal contact between the monitor and the investigator throughout the clinical investigation. The monitor should visit the investigator at the site of the investigation frequently enough to assure that:

the facilities used by the investigator continue to be acceptable for purposes of the study;

the study protocol or investigational plan is being followed;

changes to the protocol have been approved by the IRB and/or reported to the sponsor and the IRB;

accurate, complete, and current records are being maintained;

accurate, complete, and timely reports are being made to the sponsor and IRB; and

the investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

Review of Subject Records

A sponsor is responsible for assuring that the data submitted to FDA in support of the safety and effectiveness of a test article are accurate and complete. The most effective way to assure the accuracy of the data is to review individual subject records and other supporting documents and compare those records with the reports prepared by the investigator for submission to the sponsor. During a periodic visit, therefore, the monitor should compare a representative number of subject records and other supporting documents with the investigator s reports to determine that:

- the information recorded in the investigator s reports is complete, accurate, and legible;
- there are no omissions in the reports of specific data elements such as the administration to any subject of concomitant test articles or the development of an intercurrent illness;
- missing visits ro examinations are noted in the reports;
- informed consent has been documented in accordance with Parts 50 and 56.

Record of On-site Visits

The monitor or the sponsor should maintain a record of the findings, conclusions, and action taken to correct deficiencies for each on-site visit of an investigator. Such a record may enable FDA to determine that a sponsor s obligations in monitoring the progress of a clinical investigation are being fulfilled. The record may include such elements as:

- the date of the visit;
- the name of the individual who conducted the visit;

- the name and address of the investigator visited; and
- a statement of the findings, conclusions, and any actions taken to correct any deficiencies noted during the visit.

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NOTICE OF AVAILABILITY OF INVESTIGATIONAL MEDICAL DEVICES (APRIL 4, 1986)

The IDE regulations (Parts 812 and 813) prohibit the promotion or test marketing of investigational medical devices. Any person wishing to make known through a notice, publication, display, mailing, exhibit, announcement, or oral presentation the availability of an investigational device for the purpose of obtaining clinical investigators to participate in a clinical study involving human subjects should:

announce the availability of the device only in medical or scientific publications or at medical or scientific conferences whose readership or audience is composed primarily of experts qualified by scientific training and experience to investigate the safety and effectiveness of devices;

state in clear terms that the purpose is only to obtain investigators and not to make the device generally available. Enrolling more investigators or subjects than is necessary to evaluate the safety and effectiveness of the device will be considered promotion or commercialization of the device. In addition, promoting the availability of the device to obtain additional sponsors may be considered promotion or commercialization of the device;

limit the information presented in any notice of availability to the following: the name and address of the sponsor, how to apply to be an investigator, and how to obtain the device for investigational use. The notice should further list the investigator's responsibilities during the course of the investigation: namely, to await IRB and FDA approval before allowing any subject to participate, to obtain informed consent from subjects, to permit the device to be used only with subjects under the investigator's supervision, to report adverse reactions, to keep accurate records, and to conduct the investigation in accordance with the signed agreement with the sponsor, the investigational plan, FDA's regulations, and whatever conditions of approval are imposed by the reviewing IRB or FDA;

use direct mailing for the sole purpose of soliciting qualified experts to conduct investiga-

tions. Note: An undirected mass mailing will not be considered an appropriate means of soliciting clinical investigators. Such a mailing will be considered promotional;

include the following statement displayed prominently and in printing at least as large as the largest printing in the notice: "Caution -- Investigational Device, Limited By Federal (or United States) Law to Investigational Use." (Note: a clear, unequivocal statement that the device is under investigation and is available only for investigational use is to be made in oral presentations);

make only objective statements concerning the physical nature of the device;

ensure that no claims are made which state or imply, directly or indirectly, that the device is reliable, durable, dependable, safe, or effective for the purposes under investigation or that the device is in any way superior to any other device;

not present comparative descriptions of the device with other devices but may include reasonably-sized drawings or photographs of the device; and

not include information regarding pricing data but may include information stating where such data may be obtained. A sponsor or an investigator should not offer volume discounts for an investigational device since FDA would regard such discounts as the promotion of an investigational device.

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FDA IRB INFORMATION SHEETS (Reissued October 1995)

The Office of Health Affairs, FDA, with the assistance of the Office of Device Evaluation, CDRH, has developed a series of information sheets to assist IRBs in their responsibilities for the protection of research subjects. The following topics specifically address medical device issues. For additional information or to obtain the complete set of the FDA IRB Information Sheets

(October 1995), contact:

Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Telephone 301-443-1382

Advertising for Study Subjects

Recruiting Study Subjects

FDA requires that an Institutional Review Board (IRB) review and have authority to approve, require modifications in, or disapprove all research activities covered by the IRB regulations [21 CFR 56.109(a)]. An IRB is required to ensure that appropriate safeguards exist to protect the rights and welfare of research subjects [21 CFR 56.107(a) and 56.111]. In fulfilling these responsibilities, an IRB is expected to review all the research documents and activities that bear directly on the rights and welfare of the subjects of proposed research. The protocol, the consent document, and, for studies conducted under the Investigational New Drug (IND) regulations, the investigator s brochure are examples of documents that the IRB should review. The IRB should also review the methods that investigators propose to use to recruit subjects.

Direct advertising for research subjects, i.e., advertising that is intended to be seen or heard by prospective subjects, is not in and of itself an objectionable recruitment practice. Direct recruiting advertisements are seen as part of the informed consent and subject selection processes. [21 CFR 50.20, 50.25, 56.111(a)(3) and 812.20(b)(11).] IRB review is necessary to ensure that the information is not misleading to subjects. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence.

When direct advertising is to be used, the IRB should review the information contained in the advertisement and the mode of its communication, to determine that the procedure for recruiting subjects is not coercive and does not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol. The IRB should review the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. When advertisements are to be taped for broadcast, the IRB should review the final audio/video tape. The IRB may review and approve the wording of the advertisement prior to

taping to preclude re-taping because of inappropriate content. The review of a taped message prepared from IRB approved text may be accomplished through expedited procedures.

No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device. Such representation would not only be misleading to subjects but would also be a violation of the Agency s regulations concerning the promotion of investigational drugs [21 CFR 312.7(a)] and of investigational devices [21 CFR 812.7(d)].

Advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" implies that all study subjects will be receiving newly marketed products of proven worth.

Advertisements should not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation. IRBs should consider if the promise of treatment without charge is coercive to financially constrained subjects. Advertisements may state that subjects will be paid, but should not emphasize the payment or the amount to be paid.

If a clinical investigator decides to begin advertising for subjects after the study has received IRB approval, the advertising may be considered as an amendment to the ongoing study. When such advertisements are easily compared to the consent, the IRB may choose to review and approve the advertisement using expedited procedures. When the comparison is not obvious or other complicating issues are involved, the advertisement should be reviewed at a convened meeting.

Generally, FDA believes that any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements. It should be noted, however, that FDA does not require inclusion of the listed items.

1. the name and address of the clinical investigator and/or research facility;

2. the condition under study and/or the purpose of the research;

3. in summary form, the criteria that will be used to determine eligibility for the study;

4. a brief list of participation benefits, if any (e.g., a no-cost health examination);

5. the time or other commitment required of the subjects; and

6. the location of the research and the person or office to contact for further information.

Also see FDA Information Sheets: “A Guide to Informed Consent Documents” and “Payment to Research Subjects.”

INVESTIGATIONAL USE OF MARKETED DEVICES - IRB INFORMATION SHEET - FEB 1989

Good medical practice and patient interests require that physicians use commercially available devices according to their best knowledge and judgment. If a physician uses a device in the practice of medicine for an indication not in the approved labeling, he or she has the responsibility to be well informed about the product, to base its use on a firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a device in this manner as part of the "practice of medicine" does not require the submission of an IDE, or review by an IRB, unless such review is required by the institution in which the device will be used.

The investigational use of an approved, marketed device differs from the situation described above. "Investigational use" suggests the use of an approved device in the context of a study protocol. When the principal intent of the investigational use of a device is to develop information about its safety or efficacy, submission of an IDE is generally required.

The investigational use of an approved marketed device requires the submission of an IDE when the principal intent of the investigational use is to develop information about the safety and efficacy of the device for uses other than which it was approved.

Payment for Investigational Products

Charging for Investigational Products

This information sheet discusses FDA policy on allowing charges for the test articles in clinical investigations and advises Institutional Review Boards (IRBs) of ethical issues that may need to be considered.

Decisions concerning charging subjects for investigational products are guided by professional ethics, institutional policies, and FDA regulations. IRBs must ensure that subjects are fully informed if they will be charged for the costs of the investigational product and/or associated treatment. IRBs must also ensure that any such charges are appropriate and equitable.

IRBs reviewing studies in which charges are proposed may wish to consider several ethical questions: Should the subject be charged for a product that is investigational, i.e., when its safety and effectiveness have not been established by the FDA? Does charging for an investigational product preclude the economically disadvantaged or the uninsured from participating in a clinical trial?

If an investigator proposes to charge subjects for the investigational drug, biologic, or device, the IRB should review and approve the charge. The FDA informed consent regulations require the consent document to include a description of any additional costs to the subject that may result from participation in the research [21 CFR 50.25(b)(3)].

An IRB reviewing proposed charges to subjects should ask whether or not FDA approved the sponsor charging the investigator for the product. Because the regulations governing drugs and biologics vary from those governing medical devices, the Agency s position on charging for investigational products will be discussed separately. Investigators may charge the subject for related treatment or for services.

1. Charging for Investigational Medical Devices and Radiological Health Products

The Investigational Device Exemptions (IDE) regulations allow sponsors to charge for an investigational device, however, the charge should not exceed an amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device [21 CFR 812.76(b)]. A sponsor justifies the proposed charges for the device in the IDE application, states the amount to be charged, and explains why the charge does not constitute commercialization [21 CFR 812.20(b)(8)]. FDA generally allows sponsors to charge investigators for investigational devices, and this cost usually is passed on to the subjects.

2. Charging for Investigational Drugs and Biologics

Under the Investigational New Drug (IND) regulations [21 CFR 312.7(d)], FDA will permit a sponsor to charge investigators for an investigational drug or biologic depending upon whether the charge is for an investigation in a clinical trial under an IND or is for an investigation for a treatment use under a treatment protocol or treatment IND. In both a clinical trial and a

treatment IND, the charge should not exceed an amount that is necessary to recover the costs associated with the manufacture, research, development, and handling of the investigational drug or biologic. FDA may withdraw authorization to charge if the Agency finds that the conditions underlying the authorization are no longer satisfied. FDA does not prohibit charging for marketed products that are used in clinical investigations.

(a) Clinical Trials Under an IND

A sponsor may not charge for an investigational drug or biologic in a clinical trial under an IND without the Agency s prior written approval. In requesting such approval, the sponsor must explain why a charge is necessary, i.e., why providing the product without charge should not be considered part of the normal cost of conducting a clinical trial. When charges are authorized by FDA, whether they are passed on to subjects of research is a matter that clinical investigators and IRBs should carefully consider.

(b) Treatment Protocol or Treatment IND

A sponsor or investigator may charge for an investigational drug or biologic for a treatment use under a treatment protocol or treatment IND provided: (1) there is adequate enrollment in the ongoing clinical investigations under the authorized IND; (2) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (3) the drug or biologic is not being commercially promoted or advertised; and (4) the sponsor is actively pursuing marketing approval with due diligence. FDA must be notified in writing prior to commencing any such charges. Authorization for charging goes into effect automatically 30 days after receipt of the information by FDA, unless FDA notifies the sponsor to the contrary.

Payment to Research Subjects

Payment to Research Subjects

The Institutional Review Board (IRB) should determine that the risks to subjects are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25 (a)(3)]. It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development. Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive. Financial incentives are often used when benefit to subjects is remote or non-existent. The amount and schedule of all payments should be presented to the IRB

at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20].

Any payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Also see FDA Information Sheets: "A Guide to Informed Consent Documents" and "Recruiting Study Subjects."

A Guide to Informed Consent Documents

The Food and Drug Administration (FDA) has regulations [21 CFR Part 50] that govern informed consent for research with products regulated by the Agency. This information sheet was developed to help clinical investigators and Institutional Review Boards (IRBs) ensure that informed consent documents comply with the FDA requirements. For studies that are subject to the requirements of the FDA regulations, the informed consent documents should meet the requirements of 21 CFR 50.20 and contain the information required by each of the eight elements of 21 CFR 50.25(a), and each of the elements of 21 CFR 50.25(b) that are appropriate to the study. Informed consent is more than just a signature on a form, it is a process of information exchange that includes, recruitment materials, written materials, verbal instructions, question/answer sessions and measures of subject understanding.

Sample or draft consent documents may be developed by a sponsor or cooperative study group, however, it is the responsibility of the approving IRB to review such consent documents and assure that the required elements are adequately addressed, that no exculpatory language is used and that the language is understandable to the subjects. The IRB should review and approve the

finalized informed consent document developed from the sample. When a short form consent document is to be used [21 CFR 50.27(b)(2)], the IRB should review and approve the written summary of the full information to be presented orally to the subject. The IRB should inform the investigator that only IRB approved documents may be used.

[Note: the wording of the regulations below are provided in *italics,* with explanatory comments following.]

21 CFR 50.20 General requirements for informed consent

Except as provided in §50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

In informed consent documents, the use of the wording, "I understand..." may be inappropriate as many prospective subjects will not "understand" the scientific and medical significance of all the statements. Consent documents are more understandable if they are written just as the clinical investigator would give an oral explanation to the subject, that is, the subject is addressed as "you" and the clinical investigator as "I/we." This second person writing style also helps to communicate that there is a choice to be made by the prospective subject. Use of first person may be interpreted as presumption of subject consent, i.e., the subject has no choice. Also, the tone of the first person "I understand" style seems to misplace emphasis on legal statements rather than on explanatory wording enhancing the subject s comprehension.

Subjects are not in a position to judge whether the information provided is complete. Subjects may certify that they understand the statements in the consent document and are satisfied with the explanation provided by the consent process. They should not be required to certify completeness of disclosure (e.g., "This study has been fully explained to me," or, "I fully understand the study").

Consent documents should not contain claims of effectiveness, explicit or implicit, that may unduly influence potential subjects. Overly optimistic representations are misleading and violate FDA regulations concerning the promotion of investigational drugs (21 CFR 312.7] or investigational devices [21 CFR 812.7(d)].

If subjects are paid for their participation in studies, the payment should accrue as the study progresses and should not be contingent upon completion of the entire study. Payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amounts paid are reasonable and the amount of any payment based upon completion should not be so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. Therefore, the amount and schedule of all payments should be presented to the IRB at the time of initial review and the IRB should determine their acceptability. The consent document should outline the schedule and conditions of earning payment.

Investigational drug and biologic studies are not officially approved by FDA. Subjects are likely to impute a greater involvement by the Agency in a research study than actually exists if phrases such as, “FDA has given permission...” or “FDA has approved...” are used in consent documents. When a sponsor submits a study to FDA as part of the initial application for an investigational new drug (IND), FDA has thirty days to review the application and place the study on “hold” if there are any obvious reasons why the proposed study should not be conducted. If FDA does not stop the sponsor within the thirty day period, they may begin the study (with IRB approval).

FDA also believes that an explicit statement that an IRB has approved solicitation of subjects to participate in research could mislead or unduly induce subjects. Subjects might think that, because the IRB had approved the research, there is no need to evaluate the study for themselves to determine whether or not they should participate.

To meet the requirements of 21 CFR 50.20, the informed consent document should be in language understandable to the subject (or authorized representative). When the consent interview is conducted in English, the consent document should be in English. When the study subject population includes non-English speaking people or the clinical investigator or the IRB anticipates that the consent interviews will be conducted in a language other than English, the IRB should require a translated consent document to be prepared and assure that the translation is accurate. As required by 21 CFR 50.27, a copy of the consent document must be given to each subject. In the case of non-English speaking subjects, this would be the translated document. While a translator may be helpful in facilitating conversation with a non-English speaking subject, routine ad hoc translation of the consent document should not be substituted for a written

translation.

If a non-English speaking subject is unexpectedly encountered, investigators will not have a written translation of the consent document and must rely on oral translation. Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented, the subject s consent will not truly be informed and may not be legally effective. If investigators enroll subjects without an IRB approved written translation, a "short form" written consent document, in a language the subject understands, should be used to document that the elements of informed consent required by 21 CFR 50.25 were presented orally. The required signatures on a short form are stated in 21 CFR 50.27(b)(2).

Even when all the subjects speak English, the IRB should ensure that technical and scientific terms are adequately explained or that common terms are substituted. The IRB should ensure that the informed consent document properly translates complex scientific concepts into simple words that the typical subject can read and comprehend.

A person who speaks and understands English, but does not read and write, can be enrolled in a study by "making their mark" on the consent document. Development of a short form or a narrative statement is not required, but there should be an impartial witness to attest to the adequacy of the consent process and to the subject s voluntary agreement. The signatures required by 21 CFR 50.27(b)(2) are necessary.

Although not addressed in the regulations, FDA believes that IRBs should consider whether to require the approval of older children before they are enrolled in a research study. For research with children, some IRBs have required that two consent documents be developed. One for obtaining the parents permission and one, which outlines the study in simplified language, for obtaining the assent of children who can understand the concepts involved.

21 CFR 50.25 Elements of informed consent

(a) Basic Elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

> *(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any products which are experimental.*

The statement that the study involves research is important because the relationship between patient-physician is different than that between subject-investigator. Any procedures relating solely to research (e.g., randomization and placebo control) should be explained to the subjects. The procedures subjects will encounter should be outlined in the consent document, or an explanation of the procedures may be attached to and referenced in the consent document.

Consent documents for studies of investigational articles should include a statement that a purpose of the study includes an evaluation of the safety of the test article. Statements that test articles are safe or statements that the safety has been established in other studies, are not appropriate when the purpose of the study includes determination of safety. In studies that also evaluate the effectiveness of the test article, consent documents should include that purpose, but should not contain claims of effectiveness.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

The risks of procedures relating solely to research should be explained in the consent document. The risks of the tests required in the study protocol should be explained, especially for tests that carry significant risk of morbidity/mortality themselves. The explanation of risks should be reasonable and should not minimize reported adverse effects.

The explanation of risks of the test article should be based upon information presented in documents such as the protocol and/or investigator s brochure, package labeling, and previous research study reports. For IND studies, the IRB should assure that the clinical investigator submits the investigator s brochure (when one exists) with the other study materials for review.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

The description of benefits to the subject should be clear and not overstated. If no direct benefit is anticipated, that should be stated. The IRB should be aware that this element includes a description not only of the benefits to the subject, but to “others” as well. This may be an issue when benefits accruing to the investigator, the sponsor, or others are different than that normally expected to result from conducting research. Thus, if these benefits may be materially relevant to the subject s decision to participate, they should be disclosed in the informed consent document.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

To enable a rational choice to participate in the research study, subjects should be aware of the full range of options available to them. Consent documents should briefly explain any pertinent alternatives to entering the study. While this should be more than just a list of alternatives, a full risk/benefit explanation of alternatives may not be appropriate to include in the written document. The person(s) obtaining the subject s consent, however, should be able to discuss available alternatives and answer questions that the subject may raise about them. As with other required elements, the consent document should contain sufficient information to ensure an informed decision.

> *(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.*

Study subjects should be informed of the extent to which the institution intends to maintain confidentiality of records identifying the subjects. In addition, they should be informed that FDA may inspect study records (which include individual medical records). If any other entity, such as the sponsor of the study, may gain access to the study records, the subjects should be so informed. The consent document may, at the option of the IRB, state that subjects names are not routinely required to be divulged to FDA. When FDA requires subject names, FDA will treat such information as confidential, but on rare occasions, disclosure to third parties may be required. Therefore, absolute protection of confidentiality by FDA should not be promised or implied. Also, consent documents should not state or imply that FDA needs clearance or permission from the subject for access. When clinical investigators conduct a study for submission to FDA, they agree to allow FDA access to the study records. Informed consent documents should make it clear that, by participating in research, the subject s records automatically become part of the research database. Subjects do not have the option to keep their records from being audited/reviewed by FDA.

> *(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.*

Informed consent documents should describe any compensation or medical treatments that will be provided if injury occurs. If specific statements cannot be made (e.g., each case is likely to require a different response), the subjects should be informed where further information may be obtained.

> *(7) An explanation of whom to contact for answers to pertinent questions about the*

research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

This requirement contains three components, each of which should be specifically addressed. The consent document should provide the name of a specific office or person and the telephone number to contact for answers to questions about: 1) the research subjects rights; 2) a research-related injury; and 3) the research study itself. It is as important for the subject to know why an individual should be contacted as it is for the subject to know whom to contact. Although a single contact might be able to fulfill this requirement, IRBs should consider requiring that the person(s) named for questions about research subjects rights not be part of the research team as this may tend to inhibit subjects from reporting concerns and discovering possible problems.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

This element requires that subjects be informed that they may decline to participate or to discontinue participation at any time without penalty or loss of benefits. Language limiting the subject s right to withdraw from the study should not be permitted in consent documents. Subjects may be informed that they may be asked to permit follow-up if they withdraw.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

A statement that there may be unforeseen risks to the embryo or fetus may not be sufficient if animal data are not available to help predict the risk to a human fetus. Informed consent documents should explain that mutagenicity (the capability to induce genetic mutations) and teratogenicity (the capability to induce fetal malformations) studies have not yet been conducted/completed in animals. [Note: The lack of animal data does not constitute a valid reason for restricting entry of women of childbearing potential into a clinical trial.] Subjects, both women and men, need to understand the danger of taking a drug whose effects on the fetus are unknown. If relevant animal data are available, however, the significance should be explained to potential subjects. Investigators should ensure that subjects who agree to enter a study fully

understand the potential risks that the study poses. If measures to prevent pregnancy should be taken while in the study, that should be explained.

FDA guidance on the inclusion of women in clinical trials [58 FR 39406] now gives IRBs broader discretion to encourage the entry of a wide range of individuals into the early phases of clinical trials. FDA urges IRBs to question any study that appears to limit enrollment based on gender and/or minority status. Statements such as, "you may not participate in this research study if you are a woman who could become pregnant" should not routinely be included in informed consent documents.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

When applicable, subjects should be informed of circumstances under which their participation may be terminated by the investigator without the subject s consent. An unexplained statement that the investigator and/or sponsor may withdraw subjects at any time, does not adequately inform the subjects of anticipated circumstances for such withdrawal.

A statement that the investigator may withdraw subjects if they do not "follow study procedures" is not appropriate. Subjects are not in a position to know all the study procedures. Subjects may be informed, however, that they may be withdrawn if they do not follow the instructions given to them by the investigator.

(3) Any additional costs to the subject that may result from participation in the research.

If the subjects may incur an expense because they are participating in the research, the costs should be explained. IRBs should consider that some insurance and/or other reimbursement mechanisms may not fund care that is delivered in a research context.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

When withdrawal from a research study may have deleterious effects on the subject s health or welfare, the informed consent should explain any withdrawal procedures that are necessary for the subject s safety and specifically state why they are important to the subject s welfare. An unexplained statement that the subject will be asked to submit to tests prior to withdrawal, does not adequately inform the subjects why the tests are necessary for the subject s welfare.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

When it is anticipated that significant new findings that would be pertinent to subject s continued participation are likely, the IRB should determine that a system, or a reasonable plan, exists to make such notification to subjects.

(6) The approximate number of subjects involved in the study.

If the numbers of subjects in a study is material to the subject s decision to participate, the subjects should be told not only the approximate number of subjects involved in the study, but also why the number of participants is important (e.g., a small number may compromise confidentiality).

Also see FDA information sheets: "A Informed Consent and the Clinical Investigator," "Evaluation of Gender Differences in Clinical Investigations," and "Significant Differences in HHS and FDA Regulations for the Protection of Human Subjects."

Informed Consent and the Clinical Investigator

Respect for human subjects rights and dignity requires that informed consent be obtained before a subject participates in any clinical investigation, and this principle forms the basis for the Agency s informed consent regulations [21 CFR Part 50]. Institutional Review Boards (IRBs), clinical investigators, and research sponsors all share responsibility for ensuring that the informed consent process is adequate.

1. General Informed Consent Requirements

The informed consent process is designed to give subjects all the information that they need to decide about participating in a study; to ensure that subjects understand the information; and to give subjects an opportunity to consider participation in the study (initially and ongoing). The process should permit the subject to ask questions and to exchange information freely with investigator. Thus, rather than an endpoint, the consent document should be the basis for a meaningful exchange between the investigator and the subject.

The general informed consent requirements are contained in 21 CFR 50.20 and are summarized below.

- Informed consent must be obtained from the subject (or the subject s legally authorized representative) before a subject can be involved in research.

- The investigator must seek consent under circumstances that give a subject sufficient opportunity to consider whether to participate and that minimize possible coercion or undue influence. Circumstances surrounding the consent process (timing, setting, who obtains the informed consent and other details) are important to the subject s ability to comprehend the information provided.

- The information given to subjects must be understandable to them. Technical and medical terminology should be avoided or must be explained, and non-English speaking subjects must have the information presented in a language that they understand.

- The informed consent document may not include exculpatory language through which the subject is made to waive or appear to waive any legal rights or releases or appears to release the investigator, the sponsor, the institution, or their agents from liability for negligence.

2. Exception from General Requirements

As described in 21 CFR 50.23, informed consent is required unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify, in writing, all of the following:

- The subject is confronted by a life-threatening situation necessitating the test article s use.

- Informed consent cannot be obtained from the subject because of an inability to communicate with or to obtain legally effective consent from, the subject. For clarification, an "inability to communicate with the subject" exists where the subject is in a coma or a state of confusion. In contrast, a subject s inability to speak a particular language would not be considered to be an "inability to communicate."

- Time is insufficient to obtain consent from the subject s legal representative.

- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject s life.

If the investigator believes that immediate use of the test article is required to preserve the subject s life and it is not possible to obtain timely certification from a physician who is not participating in the study, the clinical investigator may proceed with its use. Following such emergency test article use, a physician who is not otherwise participating in the study must review and evaluate, in writing, the use.

When an emergency use without informed consent has occurred, the investigator must submit the certification or the evaluation to the IRB within 5 working days after the test article s use. The IRB Chair should review this documentation and, at the next convened meeting, the full IRB should be made aware of the use.

3. Documentation of Informed Consent

The informed consent documentation requirements [21 CFR 50.27] permit the use of either a written consent document that embodies the elements of informed consent or a "short form" stating that the elements of informed consent have been presented orally to the subject. Whichever document is used, a copy must be given to the person signing the document. While not specifically mentioned in the FDA regulations, the signature on the consent document should be dated at the time the subject signs, to permit verification that consent was actually obtained

before the subject s participation in the study.

When the “short form” method is used, the regulations require an IRB review and approval of a written summary of the information to be presented to subjects. A witness is required to attest to the adequacy of the consent process and to the subject s voluntary consent. The subject or the subject s legally authorized representative must sign the short form. The witness must sign both the short form and a copy of the summary, and the person actually obtaining the consent must sign a copy of the summary. The subject or the representative must be given a copy of the summary as well as a copy of the short form.

21 CFR 56.109 permits the IRB to waive, for some or all subjects, the requirement that the subject sign a written consent document if the IRB finds that:

- the research presents no more than minimal risk of harm to subjects, as defined by 21 CFR 56.102(I), and

- involves only procedures for which written consent is not normally required outside the research context.

The Agency s regulations do not permit the waiver or alteration of any of the elements of informed consent. In cases where the documentation requirement is waived, the IRB may require that the investigator provide subjects with a written statement regarding the research.

Many IRBs have developed standard language and/or a standard format to be used in portions of all consent documents. Standard language is typically developed for those elements that deal with confidentiality, compensation, answers to questions, and the voluntary nature of participation. Each investigator should determine the local IRB s requirements before submitting a study for initial review. Where changes are needed from the standard paragraphs or format, the investigator can save time by anticipating the local IRB s concerns and explaining in the submission to the IRB why the changes are necessary.

While the regulations do not prohibit the use of multiple consent documents, FDA suggests that they be used with caution. The Agency has no objection to the process of “re-consenting” subjects over time, which may be appropriate for certain types of studies. Multiple consent documents may be confusing to a research subject and if, inadvertently, one document is not presented, critical information may not be relayed to the research subject. For some studies, however, the use of multiple documents may improve subject understanding by “staging” information in the consent process. This process may be useful for studies with separate and

distinct, but linked, phases through which the subject may proceed. If this technique is used, the initial document should explain that subjects will be asked to participate in the additional phases. It should be clear whether the phases are steps in one study or separate but interrelated studies.

4. Responsibility for the Consent Document Information

The elements of informed consent are listed in 21 CFR Part 50.25. Clinical investigators should ensure that consent documents include information that either reflects or refers to all the basic elements of informed consent. The additional elements of informed consent must be included when they are appropriate to the study being described. IRBs are responsible for ensuring the adequacy of the information in the informed consent document.

Investigational New Drug Applications (INDs) submitted to FDA are not required to contain a copy of the consent document. If the sponsor submits a copy, or if FDA requests a copy, the Agency will review the document and may comment on the document s adequacy.
For significant risk medical devices, the consent document is considered to be a part of the investigational plan in the Application for an Investigational Device Exemptions (IDE). FDA always reviews these consent documents. The Agency s review is generally limited to ensuring the presence of the required elements of informed consent and the absence of exculpatory language. Any substantive changes to the document made by an IRB must be submitted to FDA (by the sponsor) for review and approval.

5. Common Problems with the Consent Document

FDA expects that consent documents will reflect, in language that is understandable to subjects, all relevant information about the study. Common problems with documents are that they:

- fail to include all the required elements specified in 21 CFR 50.25
- fail to explain technical/scientific language
- fail to state that the drug, biologic or device is experimental
- fail to state all the purposes of the research, e.g., they include only those purposes that would be considered by the subject to be “most beneficial”
- fail to state the expected duration of the subject s participation

- overstate facts or are overly optimistic in tone or wording (e.g., “this product has been extensively and safely used...”)

- fail to completely describe the procedures to be followed

- fail to adequately describe the treatment alternatives available to the subject or the risks or benefits of the alternatives

- fail to describe accurately the extent to which confidentiality will be maintained or they fail to advise the subject that FDA may inspect the records

- fail to describe the manner of payment, if any, to subjects

- fail to provide a contact for answers to questions about the research, research subjects rights, and research-related injury to the subject (a general offer to answer questions is not adequate). The contact names, telephone numbers, and addresses (when appropriate) should be included.

- fail to include “additional elements of informed consent” when those elements are appropriate, or include certain elements when they are inappropriate

- omit a written summary of what is to be said to the subject for IRB review when “short form” written consent documents are to be presented orally to subjects, or fail to provide the written summary to research subjects

- do not contain study-specific information (e.g., they are non-specific “boiler-plate” forms)

- fail to obtain IRB review and approval before use.

6. The Consent Process

The clinical investigator is responsible for ensuring that informed consent is obtained from each research subject before that subject participates in the research study. FDA does not require the investigator to personally obtain the informed consent. Investigators may ensure that an individual knowledgeable about the research presents the information to each subject, that each subject understands the information, and that subjects sign a consent document. The investigator remains ultimately responsible, even when delegating the task of obtaining informed consent. Dated signatures permit verification that consent was obtained before the subject s participation in the study. A copy of the consent document must be provided to the subject and the investigator

should retain the signed consent document in the study records. Note, that the subject s copy does not need to be a signed copy.

The IRB should be aware of who will obtain informed consent. The IRB should also be informed of such matters as the timing of obtaining informed consent and of any waiting period (between informing the subject and obtaining the consent) that will be observed.

The consent process begins when a potential research subject is initially contacted. Although an investigator may not recruit subjects to participate in a research study before the IRB reviews and approves the study, an investigator may query potential subjects to determine if an adequate number of potentially eligible subjects is available.

7. Requirements for Foreign Studies

Studies conducted under an IND or IDE in a foreign country are required to conform to the requirements of 21 CFR Parts 50 and 56. Foreign studies that are not intended for submission to FDA, i.e., not conducted under an IND or IDE, may not have conformed to these requirements. If the results from such studies are later submitted to FDA in support of a marketing permit or a premarket approval application, the Agency will require that the study conformed, at least, with the Declaration of Helsinki and/or the laws of the foreign country in which the research was conducted, whichever affords the greater protection of the human subjects. [See 21 CFR 312.120 and 21 CFR 814.15.]

The Declaration of Helsinki sets forth twelve basic principles. Two are especially relevant to informed consent:

> In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or consent to participation at any time. The physician should then obtain the subject s freely-given informed consent, preferably in writing.
>
> When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

Although the Declaration of Helsinki does not require IRB review of research by name, it does state that:

> The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

Also see FDA information sheets: "A Guide to Informed Consent Documents," "Sponsor-Investigator-IRB Interrelationship," "Acceptance of Foreign Clinical Studies," "Emergency Use of an Investigational Drug or Biologic," "Emergency Use of Unapproved Medical Devices," "Screening Tests Prior to Study Enrollment," "Recruiting Study Subjects," "Payment to Research Subjects," and "Significant Differences in HHS and FDA Regulations for the Protection of Human Subjects."

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WAIVER FOR ADDITIONAL INVESTIGATIONAL SITES (EXCERPT FROM THE IDE FORM LETTER TO A SPONSOR)

FDA will waive those requirements regarding submission and prior FDA approval of a supplemental application and receipt of certification of institutional review board (IRB) approval for the addition of investigational sites [21 CFR 812.35(b)] provided:

1. The total number of investigational sites does not exceed **[##]** (number is provided by the submitter).

2. You maintain current records on:

    a. the names and addresses of all investigational sites,
    b. the names and addresses of all investigators, identifying those who are currently participating,
    c. the names, addresses and chairpersons of all IRBs,
    d. the dates of IRB approvals, and
    e. the dates of first shipment or first use of investigational devices for all participating institutions.

3. Within 5 days of reaching the investigational site limit, you submit to FDA a current list containing the information specified in 2(a-e) above.

4. The current investigator list to be submitted to FDA at 6-month intervals [21 CFR 812.150(b)(4)] will contain the information specified in 2(a-e) above.

5. You submit to FDA, within 2 days of receipt of a request by FDA, a current list containing the information specified in 2(a-e) above.

6. The reviewing IRB does not require any significant changes in the investigational plan or in the informed consent, that is, require any change which may increase the risks to subjects or affect the scientific soundness of the study. (Please note: If a significant change is requested, this change must be submitted to FDA for review and approval prior to initiating the study at that investigational site.) Minor changes requested by the IRB may be made without prior FDA approval.

If you agree to these conditions, you may begin an investigation at a new investigational site after the IRB has approved the investigation. No documentation should be submitted for any institution within the approved limit until the investigational site limit is reached or the 6-month current investigator list is due. FDA assumes that you have agreed to the conditions of this waiver unless you specifically notify us in writing of your disagreement. Please note, however, that you must submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation beyond the limit specified above. Additionally, if you do not agree to these conditions, you must comply with the full requirements for the submission to FDA of a supplemental IDE application for new investigational sites not already specifically approved for participation in your study (21 CFR 812.35(b)).

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GUIDANCE FOR EMERGENCY USE OF UNAPPROVED MEDICAL DEVICES (OCTOBER 22, 1985)

This guidance applies to the emergency use of an unapproved medical device. For the purpose of the guidance, an unapproved medical device is a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval or an approved application for an IDE. An unapproved device may be used in human subjects only if it is approved for clinical testing under an IDE. An emergency need to use an unapproved device may occur when an IDE for the device does not exist, when a physician wants to use the device in a way not approved under the IDE, or when a physician or institution is not

approved under the IDE.

In an orderly developmental process, the developer of a device (a physician, scientist, or manufacturer) anticipates the need to conduct clinical studies and uses the IDE to ensure that adequate preclinical testing has been done, that the appropriate subjects will be selected, that subjects participate only after providing informed consent, that the device will be used properly, that subjects will be monitored adequately after the device is used, and that complete scientific data will be collected promptly. These data form the basis for subsequent marketing approval of the device.

FDA recognizes that even during the earliest phases of device design, development, and testing, emergencies arise where an unapproved device offers the only alternative for saving the life of a dying patient, but an IDE has not yet been approved for the device or the use, or an IDE has been approved but the physician who wishes to use the device is not an investigator under the IDE. Using its enforcement discretion, FDA will not object if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to FDA that an emergency actually existed.

Each of the following conditions should exist for a situation to be considered an emergency:

the patient is in a life-threatening condition that needs immediate treatment;
no generally acceptable alternative for treating the patient is available; and
because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. FDA further expects the physician not to conclude that an "emergency" situation exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than remains. Physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

In the event that a device is used in circumstances meeting the criteria listed above, FDA would expect the physician to follow as many patient protection procedures as possible. These include obtaining:

an independent assessment by an uninvolved physician;

informed consent from the patient or a legal representative;
institutional clearance as specified by institutional policies;
the IRB chairperson's concurrence; and
authorization from the sponsor, if an approved IDE for the device exists.

FDA would not object if an unapproved device were shipped without FDA approval to a physician who claims to be faced with, and describes, the kind of emergency situation discussed above. The person shipping the device should notify FDA, by telephone at 301-594-1190, immediately after shipment is made. An unapproved device may not be shipped in anticipation of an emergency.

After an unapproved device is used in an emergency the physician should:

notify the IRB and otherwise comply with provisions of the IRB regulation (Part 56) and the informed consent regulation (Part 50);

evaluate the likelihood of a similar need for the device in the future. If it is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use;

if an IDE exists, notify the sponsor of the emergency use of the device. The sponsor must comply with the reporting requirements of the IDE regulations; and

if an IDE does not exist, notify FDA of the emergency use of the device and provide FDA with a written summary of the conditions constituting the emergency, patient protection measures, and any scientific results.

Subsequent use of the device in an emergency situation may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist. Developers of devices that could be used in emergencies should anticipate the likelihood of emergency uses and should obtain an approved IDE. FDA will consider taking regulatory action if an unapproved device is used in inappropriate situations.

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STATISTICAL GUIDANCE FOR CLINICAL TRIALS
OF NON-DIAGNOSTIC MEDICAL DEVICES

The Division of Biostatistics
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
U.S. Food and Drug Administration
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I. INTRODUCTION

The collection and evaluation of sound clinical data are the basis of the approval process for many medical devices. The determination of the need for clinical data is made by the Center for Devices and Radiological Health (CDRH) based on requirements described elsewhere (DHHS, 1987; DHHS, 1990; DHHS, 1992). This guidance document assumes that the need for a clinical trial has been determined and describes procedures to assure that data from such studies can be interpreted in both a scientific and regulatory manner by the Food and Drug Administration (FDA, or the Agency).

This document is consistent with previously published clinical study guidance (DHHS, 1987; DHHS, 1990; DHHS, 1992) but provides a more comprehensive treatment of the clinical trial process from a statistical perspective. An accompanying guidance covers clinical aspects of device trials. This guidance describes how a sponsor should proceed to properly design and conduct a clinical trial in order to provide a meaningful evaluation and interpretation of clinical data in support of medical device Premarket Approval Applications (PMA).

The development of this clinical trial guidance resulted from a concern about the quality of clinical trials submitted to the Agency in support of medical device applications. This concern applied to many critical elements of clinical trial design, conduct, and analysis and was supported by the findings of the Committee for Clinical Review chaired by Dr. Robert Temple, Ann Witt served as co-chair, whose report became publicly available in March 1993. The CDRH recognized the need for a separate guidance document to address these concerns, and to clearly document those elements needed for a well designed, conducted, and analyzed device clinical trial.

The purpose of this document is to discuss important clinical trial issues and not to describe the contents of a medical device submission. It provides an explanation of each particular trial element and discusses why it should be incorporated into the clinical trial and what problems may be encountered if it is not included in the investigation.

The goal of a good clinical trial is to provide the most objective evaluation of the safety and effectiveness of the medical device based on its intended claims. Anything in the design, conduct, and analysis which impairs that objective assessment lessens the ability of the Agency staff and their advisory committees to make an informed decision concerning a "reasonable assurance of safety and effectiveness" for a device.

The cost of any decision in the design, conduct, and analysis of device clinical trials which may interfere with this objectivity must be weighed against the cost of delays or disapprovals in the

review process encountered as a result of those decisions.

While this guidance serves as a road map and provides the key elements of good clinical trial design, conduct, and analysis, it is by no means exhaustive. Numerous books, only a few of which have been referenced here, exist on the topic of clinical trial design and the scientific literature is rich with papers on the topic.

II. VALID SCIENTIFIC EVIDENCE

While the manufacturer may submit any evidence to convince the Agency of the safety and effectiveness of its device, the Agency may rely only on valid scientific evidence as defined in the PMA regulation section entitled, "Determination of Safety and Effectiveness" (21 CFR 860.7). A thorough reading of that section is strongly recommended. It should be noted that while the Agency does not prescribe specific statistical analyses for given devices and/or situations, all statistical analyses used in an investigation should be appropriate to the analytical purpose, and thoroughly documented.

"Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is a reasonable assurance of safety and effectiveness of a device under its conditions of use "(GPO, 1993).

The regulation further states, "The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations as defined in paragraph (f) of this section (860.7) unless the Commissioner authorizes the reliance upon other valid scientific evidence which the Commissioner has determined is sufficient evidence from which to determine the effectiveness of the device even in the absence of well-controlled investigations" (GPO, 1993). From these passages it is clear the Agency intends to require well-controlled clinical trials to provide the required reasonable assurance of safety and effectiveness for medical devices.

DEFINITION OF CLINICAL TRIAL

"A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against a control in human subjects" (Friedman et al., 1985). In this definition, intervention is used in the broadest sense to include "prophylactic, diagnostic, or therapeutic agents, device regimens, procedures etc." (Friedman et al, 1985).

Additional insight into clinical trials is given in a definition by Hill (1967), "The clinical trial is a carefully, and ethically, designed experiment with the aim of answering some precisely framed question." So, the clinical trial is an ethical experiment in humans and as such requires informed consent and Institutional Review Board (IRB) approval. Such considerations require careful deliberation in the design and conduct of trials. (This will be further addressed in the accompanying section on clinical aspects of trials.)

III. DESIGN OF THE CLINICAL TRIAL

A good clinical trial design controls or minimizes known or suspected sources of bias and other errors so that clinical device performance may be assessed clearly and objectively. **Error** is the result of our inability to accurately measure a variable. **Bias** results when any characteristic of the investigator, study population, or study conduct interferes in a systematic way with the ability to measure a variable accurately.

A. The Trial Objective (The Research Question)

An effective and efficient design of a clinical investigation cannot be accomplished without a clear and concise objective. Usually the study objective is posed as a research question, involving the medical claims for the device. This research question should be formulated with extreme care and specificity. A question such as "Is my device safe and effective?" is far too general to be meaningful.

The question must be refined to effectively evaluate a particular type of intervention. What is the proper way to evaluate effectiveness in the target condition and population? What are the unique safety concerns of the device intervention? Is the device as effective or more effective than another intervention? If so, is it as safe or safer? Is the evaluation of safety and effectiveness limited to a particular subgroup of patients? What is the best clinical measure of safety and effectiveness?

The attempt to answer these and similar questions will provide an essential focus to the trial and should provide the basis for labeling indications. For example, if a new device has been developed to treat a progressive, degenerative ophthalmic disorder for which there currently exists an alternative therapy using an approved device, how should effectiveness be determined? Does the new device slow or halt degeneration? If so, does it restore functions that had previously been lost? Does it reduce pain or discomfort? Is it to be compared with the approved device and is it thought to be as good as or better than the old device for some purpose? Does it have fewer adverse reactions?

One can see that asking these questions will lead not only to a focused study objective, but also will require the sponsor to consider a number of other issues, such as a suitable endpoint or outcome variable, a control population, the type of hypothesis that might be tested and others. These issues must be addressed prior to protocol development, because one must determine if the stated research question can be adequately addressed by designing a sound clinical trial. That is, can we obtain specific and objective answer(s) to the research question(s) by the collection, analysis, and interpretation of data from the clinical trial.

B. Pilot or Feasibility Study

If a sponsor cannot answer the key questions necessary to focus the trial because of insufficient experience with the device in human populations, then the sponsor should design a limited human study to gather essential information. The purpose of this limited study (frequently called a pilot or feasibility study) is to identify possible medical claims for the device, monitor potential study variables for a suitable outcome variable, test study procedures, refine the prototype device, and determine the precision of those potential response variables. It may also allow a limited evaluation of factors that may introduce bias. A protocol for a pilot study should be submitted to the Agency, usually as an Investigational Device Exemption (IDE) application.

Pilot studies are often used to field test the device. That is, the sponsor has a good idea of the utility of the device and may need a limited trial to test a theory or new technique, but the pilot study should not be too broad, i.e., a "fishing expedition". A number of issues related to the clinical trial can be refined including device use, patient processing and monitoring, data gathering and validation, and physician capabilities and concerns. Care should be taken to refine the measurements of critical variables, including potential outcome variables and influencing variables including potential sources of bias. However, it should be noted that in situations where long-term endpoints are needed, these are usually not part of the pilot study.

Pilot studies allow for limited hypothesis testing and are the ideal place for exploratory data analyses, i.e., looking for meaningful relationships between the device and outcome variables since exploratory methods will often yield research questions that can be evaluated during the clinical trial.

C. Identification and Selection of Variables

The observations in a clinical study involve two types of variables: outcome variables and influencing variables. Outcome variables define and answer the research question and should have

direct impact on the claims for the device. These variables, also known as response, endpoint, or dependent variables, should be directly observable, objectively determined measures subject to minimal bias and error. They should be directly related to biological effects of the clinical condition and this relationship itself may need validation. For example, it may be necessary to perform preliminary laboratory, animal, or limited human studies to determine that reducing a particular blood value is in fact clinically meaningful before attempting to study a device that claims to be safe and effective in decreasing this value to specific levels.

Influencing variables, also known as baseline variables, prognostic factors, confounding factors, or independent variables, are any aspect of the study that can affect the outcome variables (increase or decrease), or can affect the relationship between treatment and outcome. Imbalances in comparison or treatment groups in influencing variables at baseline can lead to false conclusions by improperly attributing an effect observed in the outcome variable to an intervention when it was merely due to the imbalance.

For example, blood pressure generally increases with age. If a group of individuals in the treatment group is significantly younger, and possess lower mean pressures than subjects in the control group, and are then compared using blood pressure as the outcome variable, the investigators may falsely conclude that an intervention was responsible for the observed "reduction" in blood pressure. Appropriate statistical testing of these baseline values should reveal any significant imbalances between the two comparison groups before the trial begins.
In the development of a clinical trial design, extreme care should be taken to identify those influencing variables that are likely to affect the outcome. By taking such known or suspected variables into consideration when designing the trial, the sponsor minimizes the chance that conclusions drawn at the end of the study will be spurious.

Once the variables or factors to be included in the trial have been identified, the selection of measurement methods becomes critical. The most informative and least subjective methods should be used. Quantitative (continuous) variables are measures of physical dimension (height, weight, circumference, area, etc.). Qualitative or categorical (discrete) variables are measures of distinct states usually represented by whole numbers (alive or dead, healthy or diseased, tumor classes, etc.).

Quantitative data can contain more information than qualitative data, and this generally allows for the use of more mathematically sophisticated and statistically powerful analytical methods. However, there may be situations where qualitative data is most appropriate or the only information available for a specific comparison, and there are many powerful non-parametric or distribution-free techniques available for these types of analyses. For example, quality of life

evaluations generally utilize these types of qualitative analytical approaches.

D. Study Population

The study population should be a representative subset of the population targeted for the application of the medical device. The study population should be defined before the trial by the development of rigorous, unambiguous inclusion/exclusion criteria. Clinical experts in the field of the device under investigation should develop these criteria. These inclusion/exclusion criteria will characterize the study population and in this way help to define the intended use for the device.

It is possible to narrowly define a study population such that it is rather homogeneous in its composition. The advantage of using a restrictive population is that it allows for a smaller sample size in the clinical trial. That is, in homogeneous populations, the variability in responses in general will be smaller than in a more heterogeneous group, and this reduction in variability, (all other critical factors being held constant), will result in a corresponding decrease in the sample size required to observe a specified significant difference between two groups.

The disadvantage is that it may limit generalization of the approval to a narrow subset of the general population as defined by the criteria. Thus, a sponsor should discuss how they intend to define the study population with the reviewing division in the Office of Device Evaluation before beginning the clinical trial.

Inclusion/exclusion criteria should include an assessment of prognostic factors for the outcome variable(s), since one or more of these variables may influence the effectiveness of the device. For example, gender may be a prognostic factor for a particular disease process. It seems reasonable then to assess what role, if any, that gender might play in device assessment and then determine inclusion/exclusion criteria, other design, and analytical considerations accordingly. Consideration should also be given to: patient age; concomitant disease, therapy or condition (at both baseline and subsequent follow-up times); severity of disease; and others.

E. Control Population

Every clinical trial intended to evaluate an intervention is comparative, and a control exists either implicitly or explicitly. The safety and effectiveness of a device is evaluated through the comparison of differences in the outcomes (or diagnosis) between the treated patients (the group

on whom the device was used) and the control patients (the group on whom another intervention, including no intervention, was used). A scientifically valid control population should be comparable to the study population in important patient characteristics and prognostic factors, i.e., it should be as alike as possible except for the application of the device.

There are many types of control groups. For the purposes of this document, four types are described:

1. Concurrent controls are those who are assigned an alternative intervention, including no intervention or a placebo intervention, and are under the direct care of the clinical study investigator. Any concurrent control can be a treatment control if it is assigned another intervention. If a placebo or sham is assigned, then it becomes a placebo or sham control. If the controls do not receive any intervention, then they are called a "no treatment" control.

2. In a passive concurrent control design, patients receive an alternative intervention, including no intervention, but are not under the direct care of the clinical study investigator.

3. Self-controls or crossover controls are patients who are assigned one intervention, (the order of treatment presentation should be specified in advance), for a prescribed period of time and then, following a washout period, receive the alternate intervention.

A washout period refers to allowing a period of time to elapse between the end of one experimental condition and the beginning of the next condition. The period of time between the two interventions should be based on current knowledge of how the device may affect any anatomical or physiological processes, so that it may be demonstrated that no residual effects of the first treatment remain which may confound the results obtained from the next scheduled treatment.

It should be noted that there will still be instances where a patient may serve as his/her own control even if a crossover design is not necessary or appropriate. For example, a crossover design would not be necessary when it can be clearly demonstrated that current clinical consensus has determined that there are no residual effects of a device beyond the immediate treatment of the patient.

4. An historical control is a nonconcurrent group of patients with the same disease or condition that have received an intervention, including no intervention, but are separated

in time and usually place, from the population under study.

Concurrent controls and, where applicable, self-controls allow the largest degree of opportunity for comparability. Passive concurrent controls can provide comparability only if the selection criteria are the same, the study variables are measured in precisely the same way as those in the study sample, and assuming there are no hidden biases.

The use of historical controls is the most difficult way to assure comparability with the study population, especially if the separation in time or place is large. The practice of medicine and nutrition is dynamic - hygiene and other factors change as well. Subtle differences (secular trends) in patient identification, concurrent therapies, or other factors can lead to differences in outcomes from a standard therapy or diagnostic algorithm. Such differences in patient selection, therapy or other factors may not be easily or adequately documented. These differences in outcome may be mistakenly attributed to a new intervention when compared to a historical control observed at a significantly different time and/or place.

In addition, it is often difficult or impossible to ascertain whether the measurement of critical study variables was sufficiently similar to those used in the current trial to allow comparison. It should not be assumed that the measurement methods are equivalent. For these reasons, historical controls will usually require much more work to validate comparability with the study population than would concurrent controls.

F. Methods of Assigning Interventions

A method of assigning treatments or interventions to patients must minimize the potential for selection bias to enter the study. Selection bias occurs when patients possessing one or more important prognostic factors appear more frequently in one of the comparison groups than in the others. For example, if we know that the mortality from a condition is twice as likely in males than in females, and that one group had a two-to-one ratio of males to females, and a second group had a two-to-one ratio of females to males, then a difference in mortality will appear between these two groups with no intervention effect. If an intervention is assigned to one of these groups, its effect on mortality will be confounded, i.e., inseparably mixed, by the effect of gender.

Appropriate steps must be taken to assure that imbalances among known or suspected prognostic factors are minimized. The preferred method for protecting the trial against selection bias is randomization. The process of randomization assigns patients to intervention or control groups such that each patient has an equal chance of being selected for each group. If the trial is large

with a limited number of comparison groups, randomization tends to guard against imbalances of prognostic factors.

It also protects the trial from conscious or subconscious actions on the part of the study investigators which could lead to non-comparability, e.g., assigning (or selecting) the most seriously ill patients to the therapy thought by the physician to be the more aggressive treatment. Finally, randomization provides a fundamental basis on which most statistical procedures are founded. Generally, randomization methods utilize random number tables, computer generated programs, etc. Specific methods of randomization with examples are discussed in textbooks on clinical trials and medical statistics (Friedman et al, 1985; Fleiss, 1986; Hill, 1967; Pocock, 1983). The method of randomization used in a trial should be specified.

On occasion, when trial sizes are small and/or the number of comparison groups is large, simple randomization may not provide adequate balance among prognostic factors within comparison groups. In such situations it may be reasonable to form subgroups, called strata, by grouping subsets of selected prognostic variables.

Other methods of treatment assignment can be devised for active concurrent controls but, unless a true randomization scheme is used, it is difficult for the sponsor to assure that the resulting assignments are free from systematic or other possible biases. For example, assigning the intervention to patients in some systematic order, say every other or every third patient, seems random. However, such periodic assignments can sometimes coincide with cyclical patterns of patient presentation at the clinic such that imbalances can occur or can lead to selection bias because the intervention assignment is predictable. Thus, systematic or patterned intervention assignments are best avoided.

The intervention assignment process should be routinely monitored to assure crude balance in the important factors that are known or suspected to affect outcome. There are grouped randomization schemes which automatically preserve balance, while other methods require monitoring and adjustment. Caution must be exercised in adjusting randomization methods to assure that the random nature is preserved. For example, some imbalance between intervention and control group is tolerable because adjustment methods exist in analysis which can be applied to make the groups comparable. Large imbalances cannot be adequately adjusted by such techniques and should be avoided by employing appropriate randomized assignment.

G. Specific Trial Designs

There are numerous trial designs available to the sponsor. The choice of a particular design depends on many factors including the hypotheses to be tested, number and impact of baseline characteristics on the outcome variable(s); number of study sites; number of therapeutic or diagnostic categories to be measured, etc. Some of the more elementary designs are discussed in this section for reference. More complete discussions of experimental designs can be found in Cox, (1958) and Cochran and Cox (1957).

The simplest and most common trial design is the parallel design. In this design, a patient series from the study population has its baseline characteristics determined, is assigned one of two or more interventions, receives the assigned intervention, and is monitored at specified times after the intervention to determine outcome. If balance is achieved in the prognostic factors and follow-up is thorough, the analysis and interpretation from a parallel design should be straightforward.

The crossover design is a modification of the parallel design with the patient used as his/her own control. In this design, each patient is assigned an order (presumably random) in which two or more interventions are to be given, followed by a period between interventions (or specimen collections) for a washout of any carry over effect from the previous intervention. These assignments should be made by randomization to protect against hidden or unknown biases. The conduct of a crossover design is somewhat more complicated than parallel designs and requires closer monitoring.

Analyses for crossover designs are also more complicated because the patient's response to any particular intervention is usually correlated with the response to another intervention. This is because more than 1 interventions are applied to the same patient and the response is likely to be influenced heavily by that patient's individual characteristics. However, patient-to-patient variability is controlled by employing a crossover design.

A third design that is applicable in medical device clinical trials is the factorial design. In a simple version of a factorial design, patients in the study population are assigned to one of four groups: one of two interventions under study, a control intervention or both interventions. Such a trial may be used if a medical device was being tested against an alternate therapy, say a drug, and the research question is to determine if either intervention acting alone was effective, or if in combination they "interacted" to produce a stronger beneficial or detrimental effect.

The negative aspect of this design is that it is more complicated to conduct and the sponsor must

assure that investigators are adhering to the study protocol.

A factorial design may require a larger sample size, but since this type of design is essentially two clinical trials in one, it offers an efficiency that should not be overlooked. If a drug intervention is proposed for a factorial design, the sponsor will have to adhere to the requirements of the Center for Drug Evaluation and Research if the drug is not already approved for the proposed claim.

Other aspects of experimental design, such as blocking or stratification, may further complicate the evaluation. The design chosen for a particular study must be the one that is most applicable to the sponsor's objectives. These objectives may appropriately result in complicated studies that need to be developed, monitored, and evaluated carefully. Sometimes, less complicated designs can be used by limiting the scope of the trial. Such a move, however, should be very carefully considered because it will nearly always result in a restriction on the claims for the device.

H. Masking (or Blinding)

Three of the more serious biases that may occur in a clinical trial are investigator bias, evaluator bias, and placebo or sham effect. An investigator bias occurs when an investigator either consciously or subconsciously favors one group at the expense of others. For example, if the investigator knows which group received the intervention, he/she may follow that group more closely and thereby treat them differently from the control group in a manner which could seriously affect the outcome of the trial.

Evaluator bias can be a type of investigator bias in which the person taking measurements of the outcome variable intentionally or unintentionally shades the measurements to favor one intervention over another. Studies that have subjective, or quality of life, endpoints are particularly susceptible to this form of bias.

The placebo or sham effect is a bias that occurs when a patient is exposed to an inactive therapy mode but believes that he/she is being treated with an intervention and subsequently shows or reports improvement.

To protect the trial against these potential biases, masking should be used. The degree of masking needed depends on the strength and seriousness of the potential bias. Single mask designs shield the patient from knowing what intervention has been assigned. Double mask trials shield both the patient and the study investigator.

Third party mask trials allow the patient and investigator to know the intervention assignment but

restrict the evaluator, i.e., the third party, from knowing, such as in the reading of imaging films or laboratory tests.

Masking is accomplished by coding the interventions and having an individual who is not on the patient care team control the key to breaking the code. The bias introduced by breaches in masking can be very difficult to assess in the analysis, therefore it is important not to break the code until the analysis is completed.

The evolution of medical device evaluation has demonstrated that it is often difficult or impossible to mask the patient or investigator because a placebo or convincing sham treatment may not be feasible. In such cases extra care must be exercised by the study staff to assure that these biases are minimized by assuring that the evaluator is blinded to the assignment of patients to a particular intervention or control group.

I. Study Site and Investigator

Because pooling of data across study sites and investigators is almost always necessary in order to attain the required sample size, the selection of study sites and investigators is critical in planning a clinical trial.

The sites that have been selected must have sufficient numbers of eligible patients who are representative of the target population for the device. Each site must have facilities that are capable of processing patients in the manner prescribed by the protocol, and must have staff who are qualified to conduct the trial. It should be noted, however, that despite a common protocol and the best efforts of the study monitor, site effects may be present which can invalidate pooling the data. A careful analysis to rule out potential bias due to site effects is an important part of the investigational protocol.

The principal investigator at each site must be able to recruit eligible patients to the trial and must be willing to abide by the procedures established by the protocol. Potential investigators may overestimate their capabilities to recruit and process study patients, so a review of the demographics and records of patients for a recent calendar period is advisable. If the investigator consistently violates the protocol, the data from that site cannot be used to establish the safety and effectiveness of the sponsor's device.

Participating physicians have a primary responsibility to their patients and must provide for individual patients what they consider to be the best medical care. While there is no question a physician must do what is best for the patient, if a specific treatment regimen happens to violate

the protocol, a patient enrolled in the study becomes disqualified from the trial and that patient's data cannot be used in the analysis.

The clinical trial is basically an experiment in a human population and as such differs from the routine practice of medicine. It should be noted that in many investigations, the Center may require an intention to treat analysis, which would record data of disqualified patients as a failure. Clearly, a relatively small number of patients that are disqualified in an intention to treat model could have a substantial impact upon the final analyses.

It should be clear, then, that deviations from the protocol by particular investigators for individual patients may create substantial problems for the trial analysis. Ultimately, it is the sponsor's responsibility to assure investigator compliance with the protocol. Potential investigators who for whatever reasons indicate that they may not be willing to strictly adhere to the protocol throughout the course of the investigation should not be asked to participate in the clinical trial.

J. Sample Size and Statistical Power

A discussion of sample size and statistical power requires knowledge of some elementary statistical principles which will be briefly reviewed here.

The object of the clinical trial is to collect data concerning the safety and effectiveness of a device in a sample of the target population. Statistical analysis is then used to infer relevant information concerning properties of the target population from the observations of those same properties in the trial sample. These inferences require that the research questions be translated into numerical statements of relationships of those population properties. Tests of the stated hypotheses should provide unequivocal answers to the research questions.

For example, if the research question is "For some disease A, is the mean value of a critical outcome variable after prescribed treatment, greater for the device-treated group than for the control group?" Two hypotheses would be formed: a null hypothesis that states that the mean value of patients post treatment in the treatment group is equal to (or worse than) that in the controls; and an alternative (or research) hypothesis that states that the mean value post treatment in the treatment group is greater than that in the controls.

There are two types of decision errors that can be made by inferring results from a sample to the population. If the sample indicates that the mean is greater in the device treated group than in the controls (i.e., rejecting the null hypothesis) when in the population there is no difference between means, a Type I error (also called an alpha error) is made. If, on the other hand, the sample

indicates no difference between means, (i.e., accepting the null hypothesis), when the device mean is actually greater, then a Type II error is made. The probability of making a Type II error is also known as Beta error, and statistical power is defined as 1 - Beta.

The probabilities of these two types of errors factor heavily into all sample size calculations for hypothesis tests (see Section VIII Appendix on Sample Size for a more thorough discussion). Usually these probabilities are fixed in advance, giving more weight to the error with the more serious consequences.

For example, a Type I error occurs if the aim of the trial is to show that the test device is "better than" the control, and we falsely reject the null hypothesis, and conclude that the device may be better than the comparison device, when in fact it is equivalent or even worse than the control. Conversely, if the object of the trial is to show that the device mean survival is "as good as" (really, "no worse than") that of the control, then it would be more serious to accept a false null hypothesis (a Type II error).

Additionally, clinical trial hypothesis tests should involve clinically meaningful differences, that is, those differences in the outcome variable(s) determined by experts in the medical community to be clinically significant. The most common sample size formulas include an estimate of the variability of the clinically meaningful difference in the numerator and an estimate of the clinically meaningful difference to be detected in the denominator. Thus, for a given outcome variable, the larger the variability, the larger the sample size that will be required. Similarly, for a given variability, the smaller the clinical difference to be detected, the larger the sample size.

Meinert (1986) provides an excellent discussion of these computations for both sample size and power.

IV. THE PROTOCOL

Each well-designed clinical trial should have a detailed protocol, i.e., the comprehensive plan that precisely describes how the trial is to be conducted and how the clinical data are to be collected and analyzed.
The protocol may be submitted to the Agency as part of an IDE or as an IDE supplement, but those study protocols not submitted as part of an IDE must be included in the submission of the PMA.

The following points should be included in the protocol and determined before initiating the trial:

1. The background of the trial that completely describes and summarizes all previous scientific studies that are pertinent to the subject matter.

2. A clear statement of the trial objective(s), specifying any medical claim and indication that is related to the research question(s), a clinically meaningful effect, and associated outcome variables.

3. A complete description of the trial design including design type, method of data collection, type of control, method and level of masking, justification of sample size, and method of treatment assignment (randomization, stratification, other).

4. A complete description of the study population, including study site(s), method of selecting subjects (inclusion and exclusion criteria), and type of patients (e.g., inpatient or outpatient). Pertinent clinical and demographic characteristics of study subjects should be discussed in relation to the characteristics of the target population and the intended use of the device (clinical utility).

5. A complete description of the intervention including frequency and duration of application, and measures of physician and patient compliance.

6. A complete description of the procedure for each follow-up visit and a schedule of required follow-up. Include identification of all measurements to be made and information collected at each visit. Also include how patient withdrawal is to be handled and those steps the sponsor will take to determine the health status of individuals who fail to return for follow-up visits or who withdraw from the study.

7. A detailed description of the data gathering and analysis, including data collection and validation methods, data monitoring, methods of statistical analysis, and specific rules as to how and why the clinical trial would be terminated early - i.e., for statistically significant un-expected positive or negative results.

8. A thorough description, including Curriculum Vitae of the participating investigators, monitoring methods, and trial administration techniques (trial monitor, policy and data monitoring committee, etc.) including methods to identify and make necessary adjustments to the protocol.

9. A list of precisely defined clinical terminology and other relevant terms to be used during the trial. This should include detailed descriptions of trial entrance criteria and

all criteria for observing either an outcome or influencing variable.

10. All informed consent forms and a list of provisions not already discussed above that may be required by the Institutional Review Board (IRB).

V. CLINICAL TRIAL CONDUCT

If a detailed protocol is established that completely describes the trial design, relevant methodologies, and the proposed analysis, then conducting the trial should be straightforward. However, it will not be simple or routine. It is imperative that those charged with the oversight of the clinical trial have contingency plans available for unforeseen problems that may occur during the trial and have means to rapidly implement those plans.

Contingency plans should be carefully crafted with the goal of preserving the integrity of the established design. Any modification of the protocol may reduce the efficiency of the design. It is difficult to envision, however, any clinical trial conducted precisely as it was designed. Therefore, it is wise to anticipate possible problems and have plans to address them if they occur.

A. Trial Monitoring

The primary concerns in conducting the clinical trial lie in assuring that the study subjects are entered, the interventions assigned, the relevant variables measured (at the appropriate times), and the data accurately and completely recorded as specified in the protocol. This requires extreme care by the trial sponsor to closely monitor the conduct of the trial. A designated trial monitor should assure compliance with the protocol and identify potential weaknesses that may require modification of the protocol.

Clinical trials generally incorporate multiple study sites with one or more investigators at each location. It is critical to the integrity of the trial that the monitor assure that each site and investigator is executing the protocol just as it was planned.

For example, if a modification of the protocol is thought to be necessary by one or more investigators and the trial is not closely monitored, it is possible that each site or investigator will modify the protocol in his/her own way. This could result in as many distinct protocol changes as there are sites or investigators, thus jeopardizing the ability to pool the trial results.

If the investigator consistently violates the protocol, the data from that site cannot be used to

establish the safety and effectiveness of the sponsor's device. To avoid this possibility, the sponsor should establish a mechanism to consider protocol modification, and appoint a monitor or gatekeeper to ensure that all sites and investigators make the same modification at the appropriate time.

B. Baseline Evaluation

Whether or not the clinical trial will use randomization, the baseline observations should be made on all prospective study patients before assigning or applying an intervention. The accurate determination of baseline information on all study subjects is critical for a number of reasons. It allows:

- the investigator to evaluate a subject's eligibility
- subclassification for stratification (if necessary)
- the descriptive characterization of the target population or an assessment that the trial sample represents the target population
- baseline physical/laboratory measurements prior to intervention

The assessment of baseline data is instrumental in the identification of prognostic factors which must be balanced among intervention groups. That is, the patient's current disease status; concomitant medication, therapy, or condition; age; gender; socioeconomic status; prior disease history; and other factors may affect the outcome variable. The assessment of baseline data allows for the selection and implementation of methods that minimize the impact of any potential bias on the comparison of outcome measures. For example, for those prognostic factors known to affect outcome, stratification or balanced allocation can be used at the time interventions are assigned.

If a prognostic factor is discovered during the course of the trial and adequate baseline measurements exist, then adjustment or standardization methods can be employed during data analysis to minimize the effect of imbalance on comparisons.

C. Intervention

The assignment and application of the intervention should be done with strict adherence to the

protocol. A pre-specified regimen should be followed on every subject. In so far as it is possible, every procedure scheduled for the treatment group should also be scheduled for the control group except for the active application of the device. If the individual administering the treatments is masked to the intervention group assignment, it is more likely that all groups will be treated the same way.

D. Follow-Up

The follow-up of subjects after intervention extends beyond the simple scheduling of follow-up appointments for the study subjects. Mechanisms should be in place to assure a high degree of subject compliance with the follow-up schedule. Even moderate deviations in follow-up between comparison groups can lead to substantial biases in the analysis.

Two characteristics of follow-up are critical: completeness and duration. Completeness is defined as the proportion of patients entering the trial who come back for each and every follow-up appointment. It is extremely important that this proportion be as close to 100% as possible, because statistical power will decrease as patients are lost to follow-up. Follow-up percentages of less than 80% are generally considered poor and these trials are labeled incomplete. It is also important for the follow-up percentages to be similar across comparison groups and across study sites.

Incomplete follow-up is a major concern in analysis. The trial must have procedures available to trace subjects who fail to appear for scheduled follow-up. Accounting for patients lost to follow-up is a critical analytical issue because those patients may provide the most important information from the clinical trial, particularly if the outcome in such patients is poor. So, it is essential to determine the health status of all patients entered into the trial even for those who do not return to the clinic for all follow-up appointments.

The duration of follow-up is that period of time after the intervention during which the study subjects are scheduled to be observed and evaluated. Follow-up duration must be consistent with safety and effectiveness claims, i.e., it must equal the duration of claimed effectiveness and must also be long enough to accurately estimate the rate of known or suspected adverse events. The duration of follow-up should also be the same across comparison groups and study sites.

E. Collection and Validation of Data

Methods for obtaining and verifying the accuracy of all measured variables in the trial must be in place before the trial begins and must be monitored for compliance. Each study site must have

sufficient staff with suitable expertise to assure the collection of valid data. Attention to detail is critical because it is impossible to retrospectively assess data not taken at the scheduled time or data taken without adequate precision.

These methods must include quality-control techniques for data measurement, recording, transfer to electronic media, and verification. The measurement of trial variables begins with an unequivocal definition of each variable, condition, or characteristic to be observed in the trial. Trial staff should completely understand all defined terms, and care must be taken to assure consistency across investigators and study sites. Consistency of trial terminology is also essential for comparisons with other trials or research studies in the literature, and for use of historical controls, where appropriate.

VI. CLINICAL TRIAL ANALYSIS

When the clinical trial reaches the analysis stage, except for deviations that may have unexpectedly occurred during the trial, the analysis should have been previously determined in the protocol. The protocol, revised by any alteration made during the trial, dictates what can or cannot be done with statistical analysis. In most cases, large biases that have been introduced by any element of trial conduct and that affect the observations of the outcome variables cannot be satisfactorily rectified by statistical adjustment procedures.

A. Validations of Assumptions

Before beginning a detailed statistical analysis it is necessary to validate the assumptions to be used in the proposed analysis. Such assumptions include underlying characteristics of the probability distribution used for hypothesis tests or estimation, similarity of distribution of prognostic factors among study sites and comparison groups, and validation of suspected relationships (dependence) or lack of relationship (independence) among variables.

It is quite important to validate the distribution and variance assumptions of the statistical test to be used. A test statistic possesses the properties of the test only if all assumptions are valid. For example, if the normal (Gaussian) distribution is assumed, the data should be tested by appropriate statistical techniques to be certain that the sample does not deviate substantially from that which would be predicted by the normal distribution. If it does, then other more appropriate tests such as non-parametric (distribution-free) procedures should be used.

Likewise if the test requires equal variance among comparison groups, an appropriate procedure

to detect unequal variances should be used. If unequal variances are detected, either the data will have to be adjusted or transformed to account for the unequal variances, or the statistical test will have to be modified.

An evaluation of the balance of prognostic factors across comparison groups and study sites is also necessary. Any observed imbalances must be adjusted so that the ultimate comparison is made between comparable samples. Analysis of covariance is a powerful statistical adjustment tool if the number of variables that require adjustment is small and the variables are highly correlated to the response variable. If the number of variables requiring adjustment is large, it is more difficult to adequately account for all of them. It is critical that extreme care be exercised in the conduct of the trial because in the words of Hill (1967) "to start out without thought and with all and sundry included, with the hope that the results can somehow be sorted out statistically in the end, is to court disaster."

If the analysis assumes that certain prognostic or response variables are unrelated to outcome, appropriate statistical tests should be performed to confirm these assumptions. Performing tests on variables that are assumed to be independent, but are in fact related, or dependent, can lead to significant errors in tests of hypotheses.

B. Hypotheses and Statistical Tests

In essence, all comparative analyses result in a hypothesis test. The report of the analysis should clearly state the hypotheses to be tested, the statistical tests to be used, and the assumptions behind the tests. All procedures should be referenced so that the Agency can validate the procedure.

References should be provided even for common procedures. If any innovative analytical procedures are developed by the sponsor, complete documentation of those procedures must accompany the analysis.

In some instances it may be appropriate to use available (historical) data to develop a mathematical model of the progression or other characteristic of a disease or condition. Data gathered in a clinical trial could be used to "validate" the model by comparing the projected characteristics of the model with results obtained during the investigation. These types of comparisons can be used to form a hypothesis test of the model characteristics.

C. Pooling

It is almost always necessary for the sponsor to pool study subjects across investigational sites in order to obtain adequate sample sizes. Pooling must be justified by testing balance among

prognostic factors and verifying that all clinical procedures were conducted in the manner prescribed in the protocol. On occasion, data from a given study site will exhibit characteristics that make it stand out from the others locations. The sponsor must investigate all relevant effects due to investigational site and report on these instances to determine why that particular site had results that differed.

D. Accountability for Patients

The sponsor should be prepared to use extensive measures to document the post-trial health status of every patient who was enrolled in the trial. While it is often not possible to find all patients, the sponsor must demonstrate that everything possible was done to attempt to find patients lost to follow-up. It is not appropriate to coerce the patient against their will to keep follow-up appointments, but, at the very least, a reasonable assessment of the morbidity or mortality of the patient should be made.

Sometimes a determination of safety and effectiveness will hinge on the differences of a small subset of patients in the comparison groups. If the number of patients lost-to-follow-up is large relative to the subset that has been observed to be different, then our ability to document safety and effectiveness is substantially weakened.

The Agency will require an analysis of the data by "intention-to-treat." This is an analysis method in which "the primary tabulations and summaries of outcome data are by assigned treatment" (Meinert, 1986). In such analyses, patients lost-to-follow-up in the intervention and control groups must be counted as though they actually completed the study in their assigned group. Since there is no observation of outcome variable after the time the patient is lost-to-follow-up, the observation cannot be counted as a success (and is considered failure).

The impact of intention-to-treat analyses on interventions that may be effective but for which there is a large number of patients lost-to-follow-up can be devastating. An observation of effectiveness in the intervention trial patients who are followed can be eclipsed entirely by a large number of patients lost to follow-up whose outcomes are recorded as ineffective. It is crucial, therefore, to keep the number of patients lost to follow-up as small as possible.

VII. BIBLIOGRAPHY

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VIII. APPENDIX ON SAMPLE SIZE

If we let p_i be the proportion surviving two years in the intervention group and p_c be the proportion surviving two years in the control group, then numerically the hypotheses are stated as:

H_o: $p_i = p_c$

H_a: $p_i > p_c$.

In the study population, one of these two conditions is true. If, based on the data, we reject H_o (and accept H_a) when H_o is true, we make a Type I statistical error. When we accept H_o (and reject H_a) based on the data when in fact H_a is true in the study population, then we make a Type II statistical error. The object of the sample size estimate is to minimize the chances of making either of these types of errors.

Probability statements are used to determine the chances of making Type I or Type II errors. The probability is based on the distribution of possible values for the outcome variable, or in the case of our example p_i or p_c.

In common statistical notation, α designates the probability of making a Type I error, i.e., the probability of rejecting the null hypothesis when it is true. The probability of the Type II error, i.e., the probability of accepting the null hypothesis when it is false, is denoted by β. The statistical power of a test method is the probability that the null hypothesis will be rejected when it is false. The power is denoted $1-\beta$.

Consider the formula for sample size for the example given here:

$$n \quad \frac{(Z_\alpha\sqrt{2pq} + Z_\beta\sqrt{(p_iq_i + p_cq_c)})^2}{d^2}$$

where n = the sample size for each comparison group.
(intervention and control)

p_i = the probability of surviving two years in the intervention group

p_c = the probability of surviving two years in the control group.

p = the mean probability of surviving two years, i.e., $(p_i + p_c)/2$

Z_α = the standard normal (Gaussian) variate corresponding to the tail probability of size α

Z_β = the standard normal variate corresponding to the tail probability of size β

d = the difference between the intervention and control groups considered to be clinically meaningful. Note $d = p_i - p_c$.

q_k = the probability of not surviving two years after treatment in the k^{th} group. Note $q_k = 1-p_k$ for k = i or c, and q = 1-p.

In most situations α and β are pre-specified to account for the seriousness of making a Type I or Type II error, respectively. By convention, α is given the value of 0.05, i.e., the chance of rejecting the null hypothesis when it is true is 1 in 20. The determination of β depends on the claim for the device. If the claim is that the two year survival of the intervention is "better than" that of the control intervention, then β can be less restrictive (meaning larger). However, it should never be greater than 0.20.

If the claim is that the two-year survival of the intervention is "as good as" (or no worse than) the control intervention, then the object would be to make β as small as feasible. When an "as good as" hypothesis is being tested, the test is attempting to "prove" the null hypotheses. The failure to reject the null hypothesis can occur under two conditions: either the two probabilities are truly not different or they are different but the sample is too small (too little power to detect the observed difference). If β is small, the power $(1-\beta)$ to detect the specified difference d is large. Under the "as good as" hypothesis it is not unusual for β to be 0.1 or even 0.05.

The difference, d, is also dependent on the claim. If the hypothesis involves the claim of "better than," then d is that increase in two year survival considered by the medical community to be

clinically meaningful. If the hypothesis involves the claim of "as good as," then d is that decrease in the two-year survival considered by the medical community to be clinically significant.

Whenever possible, the determination of d should be based on previous data. Where data are not available, it may be necessary to convene a panel of medical experts to provide a value for d which is considered by the panel to be reasonable. In either situation, the sponsor should provide a detailed justification for the choice of the d used in the calculation.

The final elements of the formula are estimates of the variability of p_i, p_c, and p. The term $\sqrt{2pq}$ involves the variability of the difference under the null hypothesis, i.e., $p_i = p_c$. The term $\sqrt{(p_iq_i + p_cq_{c)}}$ is the variability of the difference under the alternate hypothesis, i.e., $p_i > p_c$.

5 BIORESEARCH MONITORING

INTRODUCTION

The Food and Drug Administration s (FDA) bioresearch monitoring program was established in 1977 by a task force which included representatives from the drug, biologics, medical device, veterinary medicine, and food areas. The need for such a program was evident in a survey of the conduct of studies involving FDA-regulated products by the FDA field inspection operation between 1972 and 1974. Following a review of the inspectional findings, the Congress mandated that FDA develop and implement an agency-wide program.

The bioresearch monitoring program at CDRH was expanded in June 1992. In May 1993 the Bioresearch Monitoring Branch became the Division of Bioresearch Monitoring in the reorganization of the Office of Compliance. The Division monitors sponsors, institutional review boards, clinical investigators, and nonclinical laboratories involved in the testing of investigational devices.

PROGRAM OBJECTIVES

The objectives of the bioresearch monitoring program are twofold: (i) to ensure the quality and integrity of data and information submitted in support of investigational and marketing clearance applications or submissions [IDEs, PMAs, and 510(k)s]; and (ii) to ensure that human subjects taking part in investigations are protected from undue hazard or risk. The Division is also charged with the implementation of the FDA's Application Integrity Policy (AIP) for medical devices and radiological health products.

The program objectives are achieved by several means which are discussed in the program functions and inspection program sections below.

PROGRAM FUNCTIONS

The Division of Bioresearch Monitoring s (DBM) operations are directed toward several program areas. These include (1) audits of clinical data contained in PMAs prior to approval; (2) data audits of IDEs or 510(k) submissions; (3) inspections of nonclinical laboratories that perform medical device related safety testing; (4) inspections of Institutional Review Boards that monitor investigational device studies; (5) enforcement of the prohibition providing education, training and guidance to regulated industry and (7) implementation of the FDA s Application Integrity Policy. Descriptions of some of these activities are summarized below:

- PMA data audits are conducted through comprehensive on-site inspections by FDA field office staff. Source data generated and collected by clinical investigators are compared with the data and information submitted by the sponsor to FDA in support of such applications. These audits help to ensure the quality and integrity of the information used by the FDA to render safety and effectiveness decisions. Additionally, FDA field staff review the appropriate records to ensure protection of the rights and welfare of the clinical research subjects participating in these studies.

- 510(k) submissions are reviewed to identify clinical data. Where clinical data exists, assignments may be issued to FDA field offices requesting audits of that data.

- Compliance with these regulations helps to ensure Good Laboratory Practice (GLP) inspections, which involve nonclinical studies, are performed with the regulations promulgated under 21 CFR Part 58 (Good Laboratory Practice for Nonclinical Laboratory Studies). Compliance with this part is intended to ensure the quality and integrity of safety data obtained from animal studies submitted to FDA.

- Nonsignificant risk (NSR) device studies are studies which do not present a potential for serious risk to the health, safety, or welfare of a subject. The Division implemented a program to identify such studies and provide inspectional coverage.

- Surveillance information received from district offices, the public, the industry, and other sources related to commercialization or promotion of investigational devices is reviewed. If the advertisements or articles deviate from the requirements set forth in 21 CFR 812.7 (Prohibition of promotion and other practices), the Division follows up by means of a letter to the promoter or a request for inspection of the responsible party.

- Implementation of the FDA's Application Integrity Policy involves investigations of sponsors

that are suspected of submitting false or misleading data to the FDA. It also includes the review, evaluation, and monitoring of validity assessments required to be completed by sponsors found guilty of fraudulent activities.

The regulations enforced by the bioresearch monitoring program for medical devices are found in four sections of the CFR:

21 CFR 812 - Investigational Device Exemptions
21 CFR 50 - Protection of Human Subjects
21 CFR 56 - Institutional Review Boards
21 CFR 58 - Good Laboratory Practice for Nonclinical Laboratory Studies

INSPECTION PROGRAMS

FDA's inspection programs include two types of assignments: routine inspections and directed inspections (sometimes termed "for cause"). The routine assignments include inspections of clinical investigators, sponsors, IRBs, or nonclinical laboratories that are randomly selected for coverage under one of four compliance programs. These assignments are issued to monitor adherence to FDA regulations.

A directed inspection is requested when some specific problem has been identified within one or all entities of the program. The problem may be observed during the review process following evaluation of data submitted in the IDE or PMA application or through verbal or written complaints from patients, physicians, or competitors. Inspections issued for PMA data audits also fall into this category.

Deviations revealed during inspections are presented in writing and discussed with the responsible individual at the close of the inspection. Once an inspection has been completed, an establishment inspection report (EIR) is prepared and submitted by the district office. This report is then reviewed and classified by the Division of Bioresearch Monitoring.

Classifications assigned to inspections indicate whether or not the establishment is operating in compliance with the regulations. The classification scheme used by FDA is as follows:

NAI - No Action Indicated
VAI - Voluntary Action Indicated
OAI - Official Action Indicated

Depending upon the assigned classification, the Division may issue an untitled letter or warning letter based upon the severity of the deviations. These letters are intended to communicate the FDA s position on a matter, but do not commit the FDA to take further enforcement action. They are issued for the purpose of achieving voluntary compliance with the expectation that a majority of firms and individuals will comply with the regulations and implement corrective actions to prevent recurrence of the deviations.

When deviations are flagrant or significantly impact the quality and/or integrity of the research data, various actions have been used by the Division to achieve compliance in the bioresearch monitoring program area. Data audits have resulted in the Division's recommendation to invoke the Application Integrity Policy against the sponsor or reject clinical research data used to support a PMA. Data audits for 510(k)s that disclosed improprieties have led the sponsor to withdraw submissions. Monitoring efforts of IDE studies have led to the Division's recommendation for withdrawal of IDEs. Inspections of violative IRBs have resulted in administrative sanctions that suspend the institution's authority to approve new studies and/or add new subjects to existing studies.

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APPENDIXES

A - PART 812 -- INVESTIGATIONAL DEVICE EXEMPTIONS

B - PART 50 -- PROTECTION OF HUMAN SUBJECTS

C - PART 56 - INSTITUTIONAL REVIEW BOARDS

D - DECLARATION OF HELSINKI

E - PREPRODUCTION QUALITY ASSURANCE PLANNING: RECOMMENDATIONS FOR MEDICAL DEVICE MANUFACTURERS

APPENDIX A - PART 812 - INVESTIGATIONAL DEVICE EXEMPTIONS

PART 812 - INVESTIGATIONAL DEVICE EXEMPTIONS

Subpart A - General Provisions

Sec.

Subpart B - Application and Administrative Action

Subpart C - Responsibilities of Sponsors

Subpart D - IRB Review and Approval

Subpart E - Responsibilities of Investigators

Subpart F - [Reserved]

Subpart G - Records and Reports

Authority: Secs. 301, 501, 502, 503, 505, 506, 507, 510, 513 - 516, 518 - 520, 701, 702, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331, 351, 352, 353, 355, 356, 357, 360, 360c - 360f, 360h - 360j, 371, 372, 374, 379e, 381); secs. 215, 301, 351, 354 - 360F of the Public Health Service Act (42 U.S.C. 216,

241, 262, 263b - 263n). Source: 45 FR 3751, Jan. 18, 1980, unless otherwise noted.

Subpart A - General Provisions

812.1 Scope.

(a) The purpose of this part is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose. This part provides procedures for the conduct of clinical investigations of devices. An approved investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device. An IDE approved under 812.30 or considered approved under 812.2(b) exempts a device from the requirements of the following sections of the act and regulations issued thereunder: Misbranding under section 502, registration, listing, and premarket notification under section 510, performance standards under section 514, premarket approval under section 515, a banned device regulation under section 516, records and reports under section 519, restricted device requirements under section 520(e), good manufacturing practice requirements under section 520(f) (unless the sponsor states an intention to comply with these requirements under 812.20(b)(3) or 812.140(b)(4)(v)) and color additive requirements under section 721.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 3751, Jan. 18, 1980, as amended at 59 FR 14366, Mar. 28, 1994]

812.2 Applicability.

(a) General. This part applies to all clinical investigations of devices to determine safety and effectiveness, except as provided in paragraph (c) of this section.

(b) Abbreviated requirements. The following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:

(i) Labels the device in accordance with 812.5;

(ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under Part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).

(iv) Complies with the requirements of 812.46 with respect to monitoring investigations;

(v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and

(vii) Complies with the prohibitions in 812.7 against promotion and other practices.

(2) An investigation of a device other than one subject to paragraph (e) of this section, if the investigation was begun on or before July 16, 1980, and to be completed, and is completed, on or before January 19, 1981.

(c) Exempted investigations. This part does not apply to investigations of the following categories of devices:

(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under Subpart E of Part 807 in determining substantial equivalence.

(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:

(i) Is noninvasive,

(ii) Does not require an invasive sampling procedure that presents significant risk,

(iii) Does not by design or intention introduce energy into a subject, and

(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(5) A device intended solely for veterinary use.

(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).

(7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

(8) An intraocular lens. An intraocular lens shall not be used unless it is subject to an approved IDE under Part 813 or an approved application for premarket approval under section 515 of the act.

(d) Limit on certain exemptions. In the case of class II or class III device described in paragraph (c)(1) or (2) of this section, this part applies beginning on the date stipulated in an FDA regulation or order that calls for the submission of premarket approval applications for an unapproved class III device, or establishes a performance standard for a class II device.

(e) Investigations subject to IND's. A sponsor that, on July 16, 1980, has an effective investigational new drug application (IND) for an investigation of a device shall continue to comply with the requirements of Part 312 until 90 days after that date. To continue the investigation after that date, a sponsor shall comply with paragraph (b)(1) of this section, if the device is not a significant risk device, or shall have obtained FDA approval under 812.30 of an IDE application for the investigation of the device.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8956, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981; 53 FR 11252, Apr. 6, 1988]

812.3 Definitions.

(a) Act means the Federal Food, Drug, and Cosmetic Act (sections 201 901, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301 - 392)).

(b) Custom device means a device that:

(1) Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist;

(2) Is not generally available to, or generally used by, other physicians or dentists;

(3) Is not generally available in finished form for purchase or for dispensing upon prescription;

(4) Is not offered for commercial distribution through labeling or advertising; and

(5) Is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the

special needs of the physician or dentist in the course of professional practice.

(c) FDA means the Food and Drug Administration.

(d) Implant means a device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. FDA may, in order to protect public health, determine that devices placed in subjects for shorter periods are also "implants" for purposes of this part.

(e) Institution means a person, other than an individual, who engages in the conduct of research on subjects or in the delivery of medical services to individuals as a primary activity or as an adjunct to providing residential or custodial care to humans. The term includes, for example, a hospital, retirement home, confinement facility, academic establishment, and device manufacturer. The term has the same meaning as "facility" in section 520(g) of the act.

(f) Institutional review board (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving subjects and established, operated, and functioning in conformance with part 56. The term has the same meaning as "institutional review committee" in section 520(g) of the act.

(g) Investigational device means a device, including a transitional device, that is the object of an investigation.

(h) Investigation means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

(i) Investigator means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(j) Monitor, when used as a noun, means an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization. Monitor, when used as a verb, means to oversee an investigation.

(k) Noninvasive, when applied to a diagnostic device or procedure, means one that does not by design or intention: (1) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or (2) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive.

(l) Person includes any individual, partnership, corporation, association, scientific or academic establishment,

Government agency or organizational unit of a Government agency, and any other legal entity.

(m) Significant risk device means an investigational device that:

(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

(n) Sponsor means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor investigator, and the employees are investigators.

(o) Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor.

(p) Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

(q) Termination means a discontinuance, by sponsor or by withdrawal of IRB or FDA approval, of an investigation before completion.

(r) Transitional device means a device subject to section 520(l) of the act, that is, a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976.

(s) Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8956, Jan. 27, 1981; 48 FR 15622, Apr. 12, 1983]

812.5 Labeling of investigational devices.

(a) Contents. An investigational device or its immediate package shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with 801.1), the quantity of contents, if appropriate, and the following statement: "CAUTION - Investigational device. Limited by Federal (or United States) law to investigational use." The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

(b) Prohibitions. The labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

(c) Animal research. An investigational device shipped solely for research on or with laboratory animals shall bear on its label the following statement: "CAUTION - Device for investigational use in laboratory animals or other tests that do not involve human subjects."

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58842, Sept. 5, 1980]

812.7 Prohibition of promotion and other practices.

A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not:

(a) Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.

(b) Commercialize an investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.

(c) Unduly prolong an investigation. If data developed by the investigation indicate in the case of a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall promptly terminate the investigation.

(d) Represent that an investigational device is safe or effective for the purposes for which it is being investigated.

812.10 Waivers.

(a) Request. A sponsor may request FDA to waive any requirement of this part. A waiver request, with supporting documentation, may be submitted separately or as part of an application to the address in 812.19.

(b) FDA action. FDA may by letter grant a waiver of any requirement that FDA finds is not required by the act and is unnecessary to protect the rights, safety, or welfare of human subjects.

(c) Effect of request. Any requirement shall continue to apply unless and until FDA waives it.

812.18 Import and export requirements.

(a) Imports. In addition to complying with other requirements of this part, a person who imports or offers for importation an investigational device subject to this part shall be the agent of the foreign exporter with respect to investigations of the device and shall act as the sponsor of the clinical investigation, or ensure that another person acts as the agent of the foreign exporter and the sponsor of the investigation.

(b) Exports. A person exporting an investigational device subject to this part shall obtain FDA's prior approval, as required by section 801(d) of the act.

812.19 Address for IDE correspondence.

All applications, supplemental applications, reports, requests for waivers, requests for import or export approval, and other correspondence relating to matters covered by this part shall be addressed to the Center for Devices and Radiological Health, Document Mail Center (HFZ - 401), Food and Drug Administration, 9200 Corporate Blvd, Rockville, MD 20850. The outside wrapper of each submission shall state what the submission is, for example an “IDE application,” a “supplemental IDE application,” or “correspondence concerning an IDE (or an IDE application).”

[45 FR 3751, Jan. 18, 1980, as amended at 53 FR 11252, Apr. 6, 1988; 55 FR 11169, Mar. 27, 1990]

Subpart B - Application and Administrative Action

812.20 Application.

(a) Submission. (1) A sponsor shall submit an application to FDA if the sponsor intends to use a significant risk device in an investigation or if FDA notifies the sponsor that an application is required for an investigation.

(2) A sponsor shall not begin an investigation for which FDA's approval of an application is required until FDA has approved the application.

(3) A sponsor shall submit three copies of a signed "Application for an Investigational Device Exemption" (IDE application), together with accompanying materials, by registered mail or by hand to the address in 812.19. Subsequent correspondence concerning an application or a supplemental application shall be submitted by registered mail or by hand.

(b) Contents. An IDE application shall include, in the following order:

(1) The name and address of the sponsor.

(2) A complete report of prior investigations of the device and an accurate summary of those sections of the investigational plan described in 812.25(a) through (e) or, in lieu of the summary, the complete plan. The sponsor shall submit to FDA a complete investigational plan and a complete report of prior investigations of the device if no IRB has reviewed them, if FDA has found an IRB's review inadequate, or if FDA requests them.

(3) A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device.

(4) An example of the agreements to be entered into by all investigators to comply with investigator obligations under this part, and a list of the names and addresses of all investigators who have signed the agreement.

(5) A certification that all investigators who will participate in the investigation have signed the agreement, that the list of investigators includes all the investigators participating in the investigation, and that no investigators will be added to the investigation until they have signed the agreement.

(6) A list of the name, address, and chairperson of each IRB that has been or will be asked to review the investigation and a certification of the action concerning the investigation taken by each such IRB.

(7) The name and address of any institution at which a part of the investigation may be conducted that has not been identified in accordance with paragraph (b)(6) of this section.

(8) If the device is to be sold, the amount to be charged and an explanation of why sale does not constitute commercialization of the device.

(9) A claim for categorical exclusion

under 25.24 or an environmental assessment under 25.31.

(10) Copies of all labeling for the device.

(11) Copies of all forms and informational materials to be provided to subjects to obtain informed consent.

(12) Any other relevant information FDA requests for review of the application.

(c) Additional information. FDA may request additional information concerning an investigation or revision in the investigational plan. The sponsor may treat such a request as a disapproval of the application for purposes of requesting a hearing under Part 16.

(d) Information previously submitted. Information previously submitted to the Center for Devices and Radiological Health in accordance with this chapter ordinarily need not be resubmitted, but may be incorporated by reference.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8956, Jan. 27, 1981; 50 FR 16669, Apr. 26, 1985; 53 FR 11252, Apr. 6, 1988]

812.25 Investigational plan.

The investigational plan shall include, in the following order:

(a) Purpose. The name and intended use of the device and the objectives and duration of the investigation.

(b) Protocol. A written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound.

(c) Risk analysis. A description and analysis of all increased risks to which subjects will be exposed by the investigation; the manner in which these risks will be minimized; a justification for the investigation; and a description of the patient population, including the number, age, sex, and condition.

(d) Description of device. A description of each important component, ingredient, property, and principle of operation of the device and of each anticipated change in the device during the course of the investigation.

(e) Monitoring procedures. The sponsor's written procedures for monitoring the investigation and the name and address of any monitor.

(f) Labeling. Copies of all labeling for the device.

(g) Consent materials. Copies of all forms and informational materials to be provided to subjects to obtain informed consent.

(h) IRB information. A list of the names, locations, and chairpersons of all IRB's that have been or will be asked to review the investigation, and a certification of any action taken by any of those IRB's with respect to the investigation.

(i) Other institutions. The name and address of each institution at which a part of the investigation may be conducted that has not been identified in paragraph (h) of this section.

(j) Additional records and reports. A description of records and reports that will be maintained on the investigation in addition to those prescribed in Subpart G.

812.27 Report of prior investigations.

(a) General. The report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation.

(b) Specific contents. The report also shall include:

(1) A bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety or effectiveness of the device, copies of all published and unpublished adverse information, and, if requested by an IRB or FDA, copies of other significant publications.

(2) A summary of all other unpublished information (whether adverse or supportive) in the possession of, or reasonably obtainable by, the sponsor that is relevant to an evaluation of the safety or effectiveness of the device.

(3) If information on nonclinical laboratory studies is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the good laboratory practice regulations in Part 58, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with this requirement does not justify failure to provide information on a relevant nonclinical test study.

[45 FR 3751, Jan. 18, 1980, as amended at 50 FR 7518, Feb. 22, 1985]

812.30 FDA action on applications.

(a) Approval or disapproval. FDA will notify the sponsor in writing of the date it receives an application. FDA may approve an investigation as proposed, approve it with modifications, or disapprove it. An investigation may not begin until:

(1) Thirty days after FDA receives the application at the address in 812.19 for the investigation of a device other than a banned device, unless FDA notifies the sponsor that the investigation may not begin; or

(2) FDA approves, by order, an IDE for the investigation.

(b) Grounds for disapproval or withdrawal. FDA may disapprove or withdraw approval of an application if FDA finds that:

(1) There has been a failure to comply with any requirement of this part or the act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA.

(2) The application or a report contains an untrue statement of a material fact, or omits material information required by this part.

(3) The sponsor fails to respond to a request for additional information within the time prescribed by FDA.

(4) There is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, or informed consent is inadquate, or the investigation is scientifically unsound, or there is reason to believe that the device as

used is ineffective.

(5) It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of:

(i) The report of prior investigations or the investigational plan;

(ii) The methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device; or

(iii) Monitoring and review of the investigation.

(c) Notice of disapproval or withdrawal. If FDA disapproves an application or proposes to withdraw approval of an application, FDA will notify the sponsor in writing.

(1) A disapproval order will contain a complete statement of the reasons for disapproval and a statement that the sponsor has an opportunity to request a hearing under Part 16.

(2) A notice of a proposed withdrawal of approval will contain a complete statement of the reasons for withdrawal and a statement that the sponsor has an opportunity to request a hearing under Part 16. FDA will provide the opportunity for hearing before withdrawal of approval, unless FDA determines in the notice that continuation of testing under the exemption will result in an unreasonble risk to the public health and orders withdrawal of approval before any hearing.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58842, Sept. 5, 1980]

812.35 Supplemental applications.

(a) Changes in investigational plan. A sponsor shall: (1) Submit to FDA a supplemental application if the sponsor or an investigator proposes a change in the investigational plan that may affect its scientific soundness or the rights, safety, or welfare of subjects, and (2) obtain FDA approval under 812.30(a) of any such change, and IRB approval when the change involves the rights, safety, or welfare of subjects (see 56.110 and 56.111), before implementation. These requirements do not apply in the case of a deviation from the investigational plan to protect the life or physical well being of a subject in an emergency, which deviation shall be reported to FDA within 5 working days after the sponsor learns of it (see 812.150(a)(4)).

(b) IRB approval for new facilities. A sponsor shall submit to FDA a certification of any IRB approval of an investigation or a part of an investigation not included in the IDE application. If the investigation is otherwise unchanged, the supplemental application shall consist of an updating of the information required by 812.20(b) and

(c) a description of any modifications in the investigational plan required by the IRB as a condition of approval. A certification of IRB approval need not be included in the initial submission of the supplemental application, and such certification is not a precondition for agency consideration of the application. Nevertheless, a sponsor may not begin a part of an investigation at a facility

until the IRB has approved the investigation, FDA has received the certification of IRB approval, and FDA, under 812.30(a), has approved the supplemental application relating to that part of the investigation (see 56.103(a)).

[50 FR 25909, June 24, 1985; 50 FR 28932, July 17, 1985]

812.38 Confidentiality of data and information.

(a) Existence of IDE. FDA will not disclose the existence of an IDE unless its existence has previously been publicly disclosed or acknowledged, until FDA approves an application for premarket approval of the device subject to the IDE; or a notice of completion of a product development protocol for the device has become effective.

(b) Availability of summaries or data.

(1) FDA will make publicly available, upon request, a detailed summary of information concerning the safety and effectiveness of the device that was the basis for an order approving, disapproving, or withdrawing approval of an application for an IDE for a banned device. The summary shall include information on any adverse effect on health caused by the device.

(2) If a device is a banned device or if the existence of an IDE has been publicly disclosed or acknowledged, data or information contained in the file is not available for public disclosure before approval of an application for premarket approval or the effective date of a notice of completion of a product development protocol except as provided in this section. FDA may, in its discretion, disclose a summary of selected portions of the safety and effectiveness data, that is, clinical, animal, or laboratory studies and tests of the device, for public consideration of a specific pending issue.

(3) If the existence of an IDE file has not been publicly disclosed or acknowledged, no data or information in the file are available for public disclosure except as provided in paragraphs (b)(1) and (c) of this section.

(c) Reports of adverse effects. Upon request or on its own initiative, FDA shall disclose to an individual on whom an investigational device has been used a copy of a report of adverse device effects relating to that use.

(d) Other rules. Except as otherwise provided in this section, the availability for public disclosure of data and information in an IDE file shall be handled in accordance with 814.9.

[45 FR 3751, Jan. 18, 1980, as amended at 53 FR 11253, Apr. 6, 1988]

Subpart C - Responsibilities of Sponsors

812.40 General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that

IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. Additional responsibilities of sponsors are described in Subparts B and G.

812.42 FDA and IRB approval.

A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation.

[46 FR 8957, Jan. 27, 1981]

812.43 Selecting investigators and monitors.

(a) Selecting investigators. A sponsor shall select investigators qualified by training and experience to investigate the device.

(b) Control of device. A sponsor shall ship investigational devices only to qualified investigators participating in the investigation.

(c) Obtaining agreements. A sponsor shall obtain from each participating investigator a signed agreement that includes:

(1) The investigator's curriculum vitae.

(2) Where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience.

(3) If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.

(4) A statement of the investigator's commitment to:

(i) Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions

of approval imposed by the reviewing IRB or FDA;

(ii) Supervise all testing of the device involving human subjects; and

(iii) Ensure that the requirements for obtaining informed consent are met.

(d) Selecting monitors. A sponsor shall select monitors qualified by training and experience to monitor the investigational study in accordance with this part and other applicable FDA regulations.

812.45 Informing investigators.

A sponsor shall supply all investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device.

812.46 Monitoring investigations.

(a) Securing compliance. A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

(b) Unanticipated adverse device effects.

(1) A sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect.

(2) A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.

(c) Resumption of terminated studies. If the device is a significant risk device, a sponsor may not resume a terminated investigation without IRB and FDA approval. If the device is not a significant risk device, a sponsor may not resume a terminated investigation without IRB approval and, if the investigation was terminated under paragraph (b)(2) of this section, FDA approval.

Subpart D - IRB Review and Approval

812.60 IRB composition, duties, and functions.

An IRB reviewing and approving investigations under this part shall comply with the requirements of Part 56 in all respects, including its composition, duties, and functions.

[46 FR 8957, Jan. 27, 1981]

812.62 IRB approval.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all investigations covered by this part.

(b) If no IRB exists or if FDA finds that an IRB's review is inadequate, a sponsor may submit an application to FDA.

[46 FR 8957, Jan. 27, 1981]

812.64 IRB's continuing review.

The IRB shall conduct its continuing review of an investigation in accordance with Part 56.

[46 FR 8957, Jan. 27, 1981]

812.65 [Reserved]

812.66 Significant risk device determinations.

If an IRB determines that an investigation, presented for approval under 812.2(b)(1)(ii), involves a significant risk device, it shall so notify the investigator and, where appropriate, the sponsor. A sponsor may not begin the investigation except as provided in 812.30(a).

[46 FR 8957, Jan. 27, 1981]

Subpart E - Responsibilities of Investigators

812.100 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with Part 50 of this chapter. Additional responsibilities of investigators are described in Subpart G.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8957, Jan. 27, 1981]

812.110 Specific responsibilities of investigators.

(a) Awaiting approval. An investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval.

(b) Compliance. An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

(c) Supervising device use. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An

investigator shall not supply an investigational device to any person not authorized under this part to receive it.

(d) Disposing of device. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

Subpart F - [Reserved]

Subpart G - Records and Reports

812.140 Records.

(a) Investigator records. A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

(1) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

(2) Records of receipt, use or disposition of a device that relate to:

(i) The type and quantity of the device, the dates of its receipt, and the batch number or code mark.

(ii) The names of all persons who received, used, or disposed of each device.

(iii) Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

(3) Records of each subject's case history and exposure to the device. Such records shall include:

(i) Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.

(ii) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

(iii) A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

(4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

(5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

(b) Sponsor records. A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:

(1) All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports.

(2) Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of

disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

(3) Signed investigator agreements.

(4) For each investigation subject to 812.2(b)(1) of a device other than a significant risk device, the records described in paragraph (b)(5) of this section and the following records, consolidated in one location and available for FDA inspection and copying:

(i) The name and intended use of the device and the objectives of the investigation;

(ii) A brief explanation of why the device is not a significant risk device:

(iii) The name and address of each investigator:

(iv) The name and address of each IRB that has reviewed the investigation:

(v) A statement of the extent to which the good manufacturing practice regulation in Part 820 will be followed in manufacturing the device; and

(vi) Any other information required by FDA.

(5) Records concerning adverse device effects (whether anticipated or unanticipated) and complaints and

(6) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

(c) IRB records. An IRB shall maintain records in accordance with Part 56 of this chapter.

(d) Retention period. An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

(e) Records custody. An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of 812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58843, Sept. 5, 1980; 46 FR 8957, Jan. 27, 1981]

812.145 Inspections.

(a) Entry and inspection. A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where

records of results from use of devices are kept).

(b) Records inspection. A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

(c) Records identifying subjects. An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

812.150 Reports.

(a) Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:

(1) Unanticipated adverse device effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

(2) Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

(3) Progress. An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

(4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 812.35(a) also is required.

(5) Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

(6) Final report. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

(7) Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

(b) Sponsor reports. A sponsor shall prepare and submit the following complete,

accurate, and timely reports:

(1) Unanticipated adverse device effects. A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

(2) Withdrawal of IRB approval. A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

(3) Withdrawal of FDA approval. A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.

(4) Current investigator list. A sponsor shall submit to FDA, at 6 month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.

(5) Progress reports. At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, the sponsor shall also submit progress reports to FDA.

(6) Recall and device disposition. A sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

(7) Final report. In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.

(8) Informed consent. A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

(9) Significant risk device determinations. If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

(10) Other. A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58843, Sept. 5, 1980; 48 FR 15622, Apr. 12, 1983]

APPENDIX B - PART 50 PROTECTION OF HUMAN SUBJECTS

PART 50 - PROTECTION OF HUMAN SUBJECTS

Subpart A - General Provisions

Subpart B - Informed Consent of Human Subjects

Subpart C - Protection Pertaining to Clinical Investigators Involving Prisoners as Subjects

Authority: Secs. 201, 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371, 376, 381); secs. 215, 301, 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b - 263n).

Source: 45 FR 36390, May 30, 1980, unless otherwise noted.

Subpart A - General Provisions

50.1 Scope.

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(I), 507(d), and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts

(e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 406, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 36390, May 30, 1980; 46 FR 8979, Jan. 27, 1981]

50.3 Definitions.

As used in this part:

(a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq. as amended (21 U.S.C. 321 -- 392)).

(b) Application for research or marketing permit includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in 170.30 and 570.30.

(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in 180.1.

(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) Data and information about an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for these drugs, described in 314.300 of this chapter.

(12) An application for a biological product license, described in part 601.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.

(15) An Application for an Investigational Device Exemption, described in part 812.

(16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.

(17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An application for premarket approval of a medical device, described in section 515.

(19) A product development protocol for a medical device, described in section 515.

(20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in 1010.4.

(22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in 1010.5.

(c) Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(I), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d) Investigator means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g.,

corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor investigator), and the employees are considered to be investigators.

(f) Sponsor investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g) Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(h) Institution means any public or private entity or agency (including Federal, State, and other agencies). The word facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

(i) Institutional review board (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(j) Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(k) Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354 - 360F of the Public Health Service Act (42 U.S.C. 262 and 263b - 263n).

(l) Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(m) Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

[45 FR 36390, May 30, 1980, as amended at 46 FR 8950, Jan. 27, 1981; 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991]

Subpart B- Informed Consent of Human Subjects

Source: 46 FR 8951, Jan. 27, 1981, unless otherwise noted.

50.20 General requirements for informed consent.

Except as provided in 50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

50.21 Effective date.

The requirements for informed consent set out in this part apply to all human subjects entering a clinical investigation that commences on or after July 27, 1981.

50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(d)(1) The Commissioner may also

determine that obtaining informed consent is not feasible when the Assistant Secretary of Defense (Health Affairs) requests such a determination in connection with the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD). DOD's request for a determination that obtaining informed consent from military personnel is not feasible must be limited to a specific military operation involving combat or the immediate threat of combat. The request must also include a written justification supporting the conclusions of the physician(s) responsible for the medical care of the military personnel involved and the investigator(s) identified in the IND that a military combat exigency exists because of special military combat (actual or threatened) circumstances in which, in order to facilitate the accomplishment of the military mission, preservation of the health of the individual and the safety of other personnel require that a particular treatment be provided to a specified group of military personnel, without regard to what might be any individual's personal preference for no treatment or for some alternative treatment. The written request must also include a statement that a duly constituted institutional review board has reviewed and approved the use of the investigational drug without informed consent. The Commissioner may find that informed consent is not feasible only when withholding treatment would be contrary to the best interests of military personnel and there is no available satisfactory alternative therapy.

(2) In reaching a determination under paragraph (d)(1) of this section that obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of military personnel, the Commissioner will review the request submitted under paragraph (d)(1) of this section and take into account all pertinent factors, including, but not limited to:

(i) The extent and strength of the evidence of the safety and effectiveness of the investigational drug for the intended use;

(ii) The context in which the drug will be administered, e.g., whether it is intended for use in a battlefield or hospital setting or whether it will be self administered or will be administered by a health professional;

(iii) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(iv) The nature of the information to be provided to the recipients of the drug concerning the potential benefits and risks of taking or not taking the drug.

(3) The Commissioner may request a recommendation from appropriate experts before reaching a determination on a request submitted under paragraph (d)(1) of this section.

(4) A determination by the Commissioner that obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of military personnel will expire at the end of 1 year, unless renewed at DOD's request, or when DOD informs the Commissioner that the

specific military operation creating the need for the use of the investigational drug has ended, whichever is earlier. The Commissioner may also revoke this determination based on changed circumstances.

[46 FR 8951, Jan. 27, 1981, as amended at 55 FR 52817, Dec. 21, 1990]

50.25 Elements of informed consent.

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new

findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

50.27 Documentation of informed consent.

(a) Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A short form written consent document stating that the elements of informed consent required by 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

Subpart C - Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects

Effective Date Note: At 46 FR 35085, July 7, l981, the effective date of Subpart C was stayed until further notice.

50.40 Applicability.

(a) The regulations in this Subpart apply to all clinical investigations involving prisoners as subjects that are regulated by the Food and Drug Administration under sections 505(I), 507(d), or 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations involving prisoners that support applications for research or

marketing permits for products regulated by the Food and Drug Administration.

(b) Nothing in this Subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects to the extent such research is limited or barred by applicable State or local law.

50.42 Purpose.

In as much as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this Subpart to provide additional safeguards for the protection of prisoners involved in activities to which this Subpart is applicable.

50.44 Restrictions on clinical investigations involving prisoners.

(a) Except as provided in 50.44(b), clinical investigations regulated by the Food and Drug Administration under sections 505(I), 507(d), and 505(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration may not involve prisoners as subjects.

(b) Clinical investigations that are regulated by the Food and Drug Administration under sections 505(I), 507(d), or 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, may involve prisoners as subjects only if the institution responsible for the conduct of the clinical investigation has certified to the Food and Drug Administration that the institutional review board has approved the clinical investigation under 50.48; and

(1)(i) In the judgment of the Food and Drug Administration, the proposed clinical investigation involves solely research on practices both innovative and accepted, which have the intent and reasonable probability of improving, the health and well-being of the subjects;

(ii) In cases in which these studies require the assignment of prisoners in a manner consistent with protocols approved by the institutional review board to control groups that may not benefit from the research, the study may proceed only after the Food and Drug Administration has consulted with appropriate experts, including experts in penology, medicine, and ethics, and has published notice in the Federal Register of its intent to approve such research; or

(2) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis, which is much more prevalent in prisons than elsewhere) provided that the Food and Drug Administration has consulted with appropriate experts, including experts in penology, medicine, and ethics, and has published notice in the Federal Register of its intent to approve such research; subject to the approval of the Food and Drug

Administration, prisoners may participate in the research even though they are assigned, in a manner consistent with protocols approved by the institutional review board, to control groups that may not benefit from the research.

50.46 Composition of institutional review boards where prisoners are involved.

In addition to satisfying any other requirements governing institutional review boards set forth in this chapter, an institutional review board, in carrying out responsibilities under this part with respect to research covered by this Subpart, shall also meet the following specific requirements:

(a) A majority of the institutional review board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the institutional review board.

(b) At least one member of the institutional review board shall be a prisoner, or a prisoner advocate with appropriate background and experience to serve in that capacity, except that if a particular research project is reviewed by more than one institutional review board, only one institutional review board need satisfy this requirement.

50.48 Additional duties of the institutional review boards where prison are involved.

(a) In addition to all other responsibilities prescribed for institutional review boards under this chapter, the institutional review board shall review clinical investigations covered by this Subpart and approve such clinical investigations only if it finds that:

(1) The research under review represents one of the categories of research permitted under 50.44(b) (1) and (2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the clinical investigation, when compared to the general living conditions, medical care, quality of food, amenities, and opportunity for earnings in prison, are not of such a magnitude that his or
her ability to weigh the risks of the clinical investigation against the value of such advantages in the limited-choice environment of the prison is impaired;

(3) The risks involved in the clinical investigation are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners; unless the principal investigator provides to the institutional review board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that research project;

(5) Any information given to subjects is presented in language which is appropriate for the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's

participation in the clinical investigation in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the clinical investigation will have no effect on his or her parole; and

(7) Where the institutional review board finds there may be need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoner s sentences, and for informing participants of this fact.

(b) The institutional review board shall carry out such other duties as may be assigned by the Food and Drug Administration.

(c) The institution shall certify to the Food and Drug Administration, in such form and manner as the Food and Drug Administration may require, that the duties of the institutional review board under this section have been fulfilled.

APPENDIX C - PART 56 - INSTITUTIONAL REVIEW BOARDS

PART 56 - INSTITUTIONAL REVIEW BOARDS

Subpart A - General Provisions

Subpart B - Organization and Personnel

Subpart C - IRB Functions and Operations

Subpart D - Records and Reports

Subpart E - Administrative Action for Noncompliance

Authority: Secs. 201, 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371, 376, 381); secs. 215, 301, 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b - 263n).

Source: 46 FR 8975, Jan. 27, 1981, unless otherwise noted.

Subpart A - General Provisions

56.101 Scope.

(a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and

Drug Administration under sections 505(i), 507(d), and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21, unless otherwise noted.

56.102 Definitions.

As used in this part:

(a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321 - 392)).

(b) Application for research or marketing permit includes:

(1) A color additive petition, described in Part 71.

(2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in 170.35.

(3) A food additive petition, described in Part 171.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in 180.1.

(5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food packaging materials, described in 406 of the act.

(6) An investigational new drug application, described in Part 312 of this chapter.

(7) A new drug application, described in Part 314.

(8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in Part 320.

(9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in Part 330.

(10) Data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs, described in 314.300 of this chapter.

(11) An application for a biological product license, described in Part 601.

(12) Data and information regarding a biological product submitted as part of the procedures for determining that licensed

biological products are safe and effective and not misbranded, as described in Part 601.

(13) An Application for an Investigational Device Exemption, described in Parts 812 and 813.

(14) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in Part 860.

(15) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in Part 861.

(16) An application for premarket approval of a medical device for human use, described in 515 of the act.

(17) A product development protocol for a medical device for human use, described in 515 of the act.

(18) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in 358 of the Public Health Service Act.

(19) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in 1010.4.

(20) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in 1010.5.

(21) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in Subpart D of Part 1003.

(c) “Clinical investigation” means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under 505(i), 507(d), or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of Part 58, regarding nonclinical laboratory studies. The terms “research”, “clinical research”, “clinical study”, “study”, and “clinical investigation” are deemed to be synonymous for purposes of this part.

(d) “Emergency use” means the use of a test article on a human subject in a life threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e) “Human subject” means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f) “Institution” means any public or private entity or agency (including Federal, State, and other agencies). The term “facility” as

used in 520(g) of the act is deemed to be synonymous with the term "institution" for purposes of this part.

(g) "Institutional Review Board (IRB)" means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase "institutional review" committee as used in 520(g) of the act.

(h) "Investigator" means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(i) "Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) "Sponsor" means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(k) "Sponsor investigator" means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

(l) "Test article" means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under 351 or 354-360F of the Public Health Service Act.

(m) "IRB approval" means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

[46 FR 8975, Jan. 27, 1981, as amended at 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991]

56.103 Circumstances in which IRB review is required.

(a) Except as provided in 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in Parts 312, 812, and 813) to

the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

(b) Except as provided in 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

[46 FR 8975, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981]

56.104 Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

Subpart B - Organization and Personnel

56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable catgory of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the instituton's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

[46 FR 8975, Jan 27, 1981, as amended at 56 FR 28028, June 18, 1991; 56 FR 29756, June 28, 1991]

Subpart C - IRB Functions and

Operations

56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

(a) Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.

(c) Except when an expedited review procedure is used (see 56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910 - 0130)

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

56.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with 50.25. The IRB may require that information, in addition to that specifically mentioned in 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with 50.27, except that the IRB may, for some or all subjects, waive the requirement that the subject or the subject's legally authorized representative sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. In cases where the documentation requirement is waived, the IRB may require the investigator to provide

subjects with a written statement regarding the research.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Food and Drug Administration has established, and published in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the *Federal Register*.

(b) An IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited review procedure set forth in 56.108(c).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Food and Drug Administration may restrict, suspend, or terminate an

institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

56.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by Part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by 50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

56.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval

or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

56.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

56.114 Cooperative research.

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

Subpart D - Records and Reports

56.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

(6) Written procedures for the IRB as required by 56.108 (a) and (b).

(7) Statements of significant new findings provided to subjects, as required by 50.25.

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910 - 0130)

[46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

Subpart E - Adminstrative Actions for Noncompliance

56.120 Lesser administrative actions.

(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.

(b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may:

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;

(2) Direct that no new subjects be added to ongoing studies subject to this part;

(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or

(4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.

(c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this Subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

56.121 Disqualification of an IRB or an institution.

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under 56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may

justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in Part 16.

(b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:

(1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and

(2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

(c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the Federal Register.

(d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in 56.123.

56.122 Public disclosure of information regarding revocation.

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under Part 20.

56.123 Reinstatement of an IRB or an institution.

An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under 56.121(c).

56.124 Actions alternative or additional to disqualification.

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of,

and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.

APPENDIX D - DECLARATION OF HELSINKI

The “Declaration of Helsinki” states as follows:

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, “The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, “A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research

involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid

down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient -- including those of a control group, if any should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non Therapeutic Biomedical Research Involving Human Subjects (Non Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers -- either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 56 FR22113, May 14,1991]

APPENDIX E - PREPRODUCTION QUALITY ASSURANCE PLANNING: RECOMMENDATIONS FOR MEDICAL DEVICE MANUFACTURERS

1.0 SCOPE

This document describes recommended design practices applicable to medical devices and is intended to assist device manufacturers in planning and implementing a preproduction quality assurance program. The purpose is to provide a high degree of confidence that medical device designs are reliable, safe, and effective prior to releasing designs to production for routine manufacturing.

The extent to which these recommendations are implemented is left to the discretion of the manufacturer, and may involve a consideration of the risk a device would present to the user if it were unsafe or ineffective. Some of the recommendations may be excessive for devices that are simple in design and present no risk to the user should they fail. However, all medical device manufacturers are encouraged to use these recommendations, especially those manufacturers who have found it necessary to recall devices from the marketplace because of defects in the design of a component, sub-assembly, or the device itself. Likewise manufacturers of life-sustaining, life-supporting, or implantable devices, particularly those who make electrical, electromechanical, or mechanical devices, are encouraged to examine these suggested practices to determine whether they are applicable to product development. Additionally, manufacturers who are committed to company-wide quality assurance programs to enhance product quality and productivity, and who wish to minimize the cost of these programs, should find all or some of these recommendations helpful in identifying the preproduction activities that FDA believes are important.

The practices described herein are applicable to the development of new designs as well as to the adaptation of existing designs to new or improved applications. The word "should" is used in the document in reference to practices and procedures which, though recommended, are nonmandatory.

2.0 INTRODUCTION

The design phase is the most important phase in the life cycle of a device. The inherent safety, effectiveness, and reliability of a device are established during this phase. No matter how carefully a device may be manufactured or how perfect the GMP program, this inherent safety and effectiveness cannot be improved except through design enhancement. Therefore, it is crucial that adequate controls be established and implemented during the design phase to assure that the safety, effectiveness and reliability of the device are optimally enhanced prior to manufacturing to

assure that an acceptable quality level can be achieved during production. It is only through careful planning and management of the preproduction process that safety, effectiveness, and reliability can be established in a device.

A design deficiency can be very costly once a device design has been released to production and the device is manufactured and distributed. Costs may include not only replacement and redesign costs, with resulting modifications to manufacturing, procedures, retraining, etc. to enable manufacture of the modified device, but also liability costs and loss of customer faith in the product.

Analysis of recall and other adverse experience data available to FDA indicates that one of the major causes of device failures is deficient design. Examples are cited herein, not as an indictment of particular manufacturers or industries, but as an illustration of the advantages of implementing a preproduction quality assurance program. The examples used are from FDA's device recall records.

3.0 PREPRODUCTION QUALITY ASSURANCE PROGRAM

All manufacturers of medical devices should establish and implement a program for assessing the reliability, safety, and effectiveness of device design prior to releasing the design to production and, ideally, this assessment should be made as the design is developed. The procedures for making these assessments should be defined in a formally established and documented preproduction quality assurance (PQA) program. Formal protocols should be developed and agreed upon for design verification and reliability assessment. The program should be sanctioned by upper management and should be considered a crucial part of each manufacturer's overall effort to produce only reliable, safe, and effective devices.

3.1 ORGANIZATION

The organizational elements and authorities necessary to establish the PQA program, to execute program requirements, and to achieve program goals should be specified in formal documentation. Responsibility for implementing the overall program and each program element should also be formally assigned and documented.

An audit program should be established as a permanent part of the PQA, and audits should be conducted periodically throughout the preproduction life cycle phase to evaluate program implementation and effectiveness. The program should be updated as experience is gained and the need for improvement is noted.

Manufacturers should consider the following activities when developing the PQA program and implement those controls most appropriate for assuring the safety, effectiveness, and reliability of the device design.

3.2 SPECIFICATIONS

Prior to the design activity, the design concept should be defined or expressed in terms of its desired characteristics, such as physical, chemical, performance, etc. Acceptable ranges or limits should be provided for each characteristic to establish allowable variations and these should be expressed in terms that are readily measurable.

Once these characteristics are agreed upon as those desired for the proposed device (i.e. the design aim), they should be translated into written design specifications. These preliminary specifications provide the details from which the design can be developed and controlled, as well as the means by which the design can be evaluated. Specifications should address, as applicable, performance characteristics, such as safety, durability/ reliability, precision, stability and purity, necessary to fulfill the product's intended purpose. The expected use of the device, the user, and user environment should be considered when establishing the design's physical configuration, performance, safety and effectiveness goals (for example, location of controls, displays, allowable leakage currents, use in the home, etc.). Specifications should be reviewed and evaluated by qualified personnel from appropriate organization elements, such as Marketing, R&D, Quality Assurance, Reliability, and Manufacturing.

3.2.1 System Compatibility

A device's compatibility with other devices in the intended operating system should be addressed early in the design phase, to the extent that compatibility is necessary to assure proper functioning of the system; examples include IV sets with infusion pumps, breathing circuits with ventilators, disposable electrodes with cardiac monitors. The full operating range of within-tolerance specifications for the mating devices(s) should be considered, not merely nominal values.

3.2.2 Design Changes

Changes made to the specifications during R&D that are accepted as design changes should be documented and evaluated to assure that they accomplish the intended result and do not compromise safety or effectiveness. Manufacturers should not make unqualified, undocumented changes during preproduction clinical trials in response to suggestions or criticisms from clinicians. In the manufacturer's haste to satisfy the user, changes made without an evaluation of

the overall effect on the device could result in improving one characteristic of the device while having an unforeseen adverse effect on another.

The documentation of changes made to a device as it is developed provides a complete history of the product design evolution and a means by which each design change can be reviewed. This documentation can be invaluable for conducting investigations of design deficiencies which may not be detected until after the finished device is in commercial distribution.

3.3 DESIGN REVIEW

Device design should progress through clearly defined and planned stages. For example, a new medical device could be designed in planned stages including concept, detail design, prototype, and pilot production. Each medical device manufacturer should establish and implement, as the cornerstone of the PQA program, an independent assessment or review of the design at each stage as the design matures to assure conformance to design criteria and to identify design weaknesses. Some manufacturers may find it advantageous to consult with outside experts. The objective of design review is the early detection and remedy of design deficiencies. The earlier design review is initiated, the sooner problems can be identified and the less costly it will be to implement corrective action. The assessment should include a formal review of subsystems, including software (when applicable), components, packaging, labeling, and support documentation such as drawings, test specifications, and instructions. The extent and frequency of design review depends on the complexity and significance of the device studied. However, the assessment should extend beyond merely satisfying user requirements and always assure that safety and effectiveness goals are met.

A detailed, documented description of the design review program should be established, including organizational units involved, procedures used, flow diagrams of the process, identification of documentation required, a schedule, and a checklist of variables to be considered and evaluated.

Reviews should be objective, unbiased examinations by appropriately trained personnel who include individuals other than those responsible for the design. For example, design review should be conducted by representatives of Manufacturing, Quality Assurance, Engineering, Marketing, Servicing, and Purchasing, as well as those responsible for R&D. Design review should, as applicable and at the appropriate stage, also include those designated to conduct and monitor preclinical and clinical studies. Provisions should be prescribed for resolving differences of technical judgment. Review results should be well documented in report form and signed by designated individuals as complete and accurate. All changes made as a result of review findings should be documented. Reports should include conclusions and recommended follow up and

should be disseminated in a timely manner to appropriate organizational elements, including management.

When corrective action is required, the action should be appropriately monitored, with responsibility assigned to assure that a follow up is properly conducted. Schedules should be established for completing corrective action. Quick fixes should be prohibited. These include adjustments that may allow the device to perform adequately for the moment but do not address the underlying cause. All design defects should be corrected in a manner that will assure the problem will not recur. Design reviews should, when determined appropriate, include failure mode effects analysis.

3.3.1 Failure Mode Effects Analysis

Failure mode effects analysis (FMEA) should be conducted at the beginning of the design effort and as part of each design review to identify potential design weaknesses. The primary purpose of FMEA is the early identification of potential design inadequacies that may adversely affect safety and performance. Identified inadequacies can then be eliminated or their effect (susceptibility) minimized through design correction or other means.

FMEA is conducted by identifying, through failure analysis techniques, significant failure modes that can occur, their effect on safety and effectiveness, and the probability of occurrence. When it is likely that a failure could adversely impact on safety or effectiveness, the design should be modified to eliminate or minimize the failure cause. For those potential failure modes that cannot be corrected through redesign effort, special controls such as labeling warnings, alarms, etc. should be provided. FMEA should include an evaluation of possible human-induced failures or hazardous situations.

Each potential failure mode should be considered in light of its probability of occurrence and characterized as to the severity of its effect on reliability, safety, and effectiveness.

FMEA should be conducted in accordance with a written protocol, with results and recommendations documented and provided to the appropriate personnel in a timely manner. When design weaknesses are identified, consideration should be made of other distributed devices in which the design weakness may also exist. Appropriate action should be taken as necessary to correct these design deficiencies.

Typically, two failure mode analysis techniques are used: (1) Fault Tree Analysis and (2) Failure Mode Effects Criticality Analysis.

3.3.1.1 Fault Tree Analysis

Fault tree analysis (FTA) is a deductive, "top-down" approach to failure mode analysis. First, a system failure or safety hazard is assumed. Next, through the use of detailed logic diagrams, basic component failures or events are simulated to determine if the hazard could actually occur. Once identified, computational techniques are used to analyze the basic defects, determine failure probabilities, and establish severity of effect levels. FTA is especially applicable to medical devices because human/device interfaces can be taken into consideration, i.e., a particular kind of adverse effect on a user such as electrical shock can be assumed. Whether or not the event can occur, either because of a defective device or operator error, can then be determined.

3.3.1.2 Failure Mode Effects Criticality Analysis

Failure mode effects criticality analysis (FMECA) is an inductive "bottom-up" process which assumes basic defects at the component level and then determines the effects on higher levels of assembly. Failure modes are analytically induced into each component and failure effects are evaluated and noted, including severity and probability of occurrence. FMECA can be performed using either actual failure data derived from field failures or hypothesized failure modes derived from design analysis or other sources. In addition to providing information about failure cause and effect, FMECA provides a structured method for proceeding component-by-component through the system to assess failure effects.

FMECA is described in MIL-STD-1629A, "Procedures for Performing Failure Mode, Effects, and Criticality Analysis," and on-site training is offered by private firms.

3.4 RELIABILITY ASSESSMENT

When appropriate and applicable, a reliability assessment should be made for new and modified designs and acceptable failure rates established. Reliability assessment is the process of prediction and demonstration directed towards estimating the basic reliability of a device. The appropriateness and extent of a reliability assessment should be determined by the risk the device presents to the user should it fail or become defective.

Prior to distribution, reliability assessment may be initiated by theoretical and statistical methods by first determining the reliability of each component, then progressing upward, establishing the reliability of each subassembly and assembly, until the reliability of the entire device or device system is established. This approach, however, provides only an estimate of reliability, since it does not simulate the actual effect of interaction of system parts and the environment. To properly estimate reliability, complete devices and device systems should be tested under simulated use conditions. The most meaningful reliability data are usually obtained

from actual use.

The process of reliability assessment goes beyond merely making a prediction, testing, and then waiting for field experience to prove or disprove the assessment. Reliability assessment is a continuous process that includes predicting, demonstrating reliability, analyzing data, then re-predicting, re-demonstrating reliability, and re-analyzing data on a continual basis. Reliability assessment should be considered an essential part of the PQA program and should be used to estimate and establish the reliability of each new and modified design, when applicable.

3.5 PARTS AND MATERIALS QUALITY ASSURANCE

All medical device manufacturers should establish and implement a comprehensive parts and materials (P/M) quality assurance program for assuring that all P/M used in device designs have the reliability necessary to achieve their intended purposes. For some this can be done in-house, while for others it may be necessary to contract with suppliers or outside test labs. The reliability goal should be based on the severity of use and importance of the P/M function. The P/M program should encompass the selection, specification, qualification and ongoing verification of P/M quality, whether fabricated in-house or provided by vendors. P/M quality assurance should include qualification of suppliers to aid in assuring only quality P/M are used.

Parts and materials should be selected on the basis of their suitability for the chosen application, compatibility with other P/M and the environment, and proven reliability. Conservative choices in selection of P/M are characteristic of reliable devices. Standard proven P/M should be used as much as possible in lieu of "unproven" P/M.

A preferred P/M list should be established during the preliminary design stage and refined as the design progresses. This list should include approved suppliers for the P/M and be placed under formal change control once the design is released for production. P/M should be classified according to the severity of their effect on reliability, safety, and effectiveness should they fail or not achieve their intended purpose. Emphasis on the use of high reliability P/M, qualification, inspection, test, and other methods of assuring acceptability should be based on this classification; i.e., more emphasis should be placed on assuring the acceptability of P/M whose failure could result in injury.

The acceptability of P/M for their selected applications should be determined and supported by both calculated and observed test data. Proper application means not only assuring P/M will perform but that they are not unduly stressed mechanically, electrically, environmentally, etc. A thorough applications review should be conducted during the design phase and, when necessary, adequate margins of safety should be established. Existing test or qualification data may be used

for proven or standard P/M. However, when selecting P/M previously qualified, attention should be given to whether the data are current, the applicability of the previous qualification to the intended application, and the adequacy of the existing P/M specification. Additional qualification should be conducted as necessary.

Failure of P/M during qualification to meet expected performance, safety, and effectiveness objectives should be investigated and the results described in written reports. These reports should be provided to management and other appropriate personnel in a timely manner to assure that only qualified P/M are used. Failure analysis, when deemed appropriate, should be conducted to a level such that the failure mechanism can be identified.

3.6 SOFTWARE QUALITY ASSURANCE

When a design incorporates software developed in-house, a software quality assurance program should be in place that outlines a systematic approach to software development. The program should include a protocol for formal review and validation of device software to ensure overall functional reliability.

There are many approaches to software quality assurance (SQA), and some of these are described in the software source documents referenced at the end of this document. However, they all involve some form of measuring the development process at each phase; for example, establishing requirements, validating that the output of each phase satisfies its requirements (which may include testing), documenting and controlling changes that are made, and revalidating. Major goals of SQA are correctness, reliability, testability, and maintainability.

SQA should begin with a plan, which can be written using a guide such as ANSI/IEEE Standard 730-1984, IEEE Standard for Software Quality Assurance Plans. Good SQA assures quality software from the beginning of the development cycle by specifying up front the required quality attributes of the completed software and the acceptance testing to be performed. In addition, the software should be written in conformance with a company standard using structured programming. The SQA representative or department should have the authority to enforce implementation of SQA policies and recommendations.

When device manufacturers purchase custom software from contractors, the SQA should assure that the contractors have an adequate SQA program that will assure software correctness, reliability, testability, and maintainability.

When manufacturers purchase "off-the-shelf" software from vendors or subcontractors, the SQA should assure, through appropriate testing, that the software is adequate for its intended

application prior to use in production.

3.7 LABELING

A review of labeling should be included as part of the design review process to assure that it is in compliance with applicable laws and regulations and that adequate directions for the product's intended use are easily understood by the end-user group. Labeling includes manuals, charts, inserts, panels, display labels, recommended test and calibration protocols, software for CRT displays, etc. Qualification testing of the device should include verification of the accuracy of instructions contained in the labeling. Qualification should also include verification that labeling intended to be permanently attached to the device will remain attached and legible through processing, storage, and handling for the useful life of the device.

Maintenance manuals should be provided where applicable and should provide adequate instructions whereby a user or service activity can maintain the device in a safe And effective condition.

3.8 DESIGN TRANSFER

Once the design is translated into physical form, its technical adequacy, safety and reliability should be verified through comprehensive documented testing under simulated or actual use conditions.

Clinical trials should not begin until the safety of the device has been verified under simulated use conditions, particularly at the expected performance limits. Simulated use testing should address use with other applicable devices and possible misuse. Manufacturers of devices that are likely to be used in a home environment and operated by persons with a minimum of training and experience should anticipate the types of operator errors most likely to occur. These manufacturers should design and label their products to encourage proper use and to minimize the frequency of misuse.

The design is typically approved after its technical adequacy has been verified through applicable testing. The design, which includes components, packaging and labeling, is then translated into approved, formal specifications. The device, however, is not yet ready to be released to manufacturing for routine production.

Before the specifications are released for routine production, actual finished devices should be manufactured using the approved specifications, the same materials and components, the same or similar production and quality control equipment, and the methods and procedures that will be

used for routine production. Typically, this is accomplished by manufacturing "pilot runs" or "first production runs." These devices should then be qualified through extensive testing under actual or simulated use conditions and in the environment, or simulated environment, in which the device is expected to be used. The extent of the testing conducted should be governed by the risk the device will present should it fail. These procedures are considered essential for assuring the manufacturing process will produce the intended devices without adversely affecting the devices and are a necessary part of process validation.

Caution should be taken when using prototypes developed in the laboratory or machine shop as qualification units. Prototypes may not be like the finished production device. During R&D, conditions are typically better controlled and personnel more knowledgeable about what needs to be done and how to do it than production personnel. When going from laboratory to scaled-up production, standards or methods and procedures may not be properly transferred or additional manufacturing processes may be added. Often changes, not reflected in the prototype, are made in the product to facilitate the manufacturing process. Proper qualification of devices that are produced using the same or similar methods and procedures as those to be used in routine production can prevent the distribution and subsequent recall of many unacceptable medical devices.

Typically, testing under use conditions is the clinical or in-vivo testing stage for devices requiring an Investigational Device Exemption (lDE), or clinical studies to support a Premarket Notification (510(k)], or Premarket Approval (PMA) submission to FDA. When practical, clinical testing should be conducted using devices produced under expected routine production conditions. Otherwise, the clinically qualified device will not be truly representative of production devices. Advice from clinicians should be sought with respect to how the device will actually be used. Testing should include stressing the device at its performance and environmental specification limits.

Testing should be performed according to a documented test plan that specifies the performance parameters to be measured, test sequence, evaluation criteria, test environment, etc. Once the device is qualified, all manufacturing and quality assurance specifications should be placed under formal change control. Storage conditions should be considered when establishing environmental test specifications.

3.9 CERTIFICATION

After initial production units have successfully passed preproduction qualification testing, a formal technical review should be conducted to assure adequacy of the design, production, and quality assurance procedures, and should include a determination of the:

- Resolution of any differences between the procedures and standards used to produce the design while in R&D and those approved for production.

- Resolution of any differences between the approved device specifications and the actual manufactured product.

- Validity of test methods used to determine compliance with the approved specifications.

- Adequacy of specifications and specification change control program.

- Adequacy of the complete quality assurance plan.

3.10 PERSONNEL

Design activities, including design review, analysis, and testing should be conducted by appropriately trained and competent personnel.

3.11 TEST INSTRUMENTATION

All equipment used in qualification of the design should be properly calibrated and maintained under a formal calibration and maintenance program.

3.12 QUALITY MONITORING AFTER THE DESIGN PHASE

Once the design has been proven safe and effective and devices are produced and distributed, the effort to assure that the device and its components have acceptable quality and are safe and effective is not complete. This effort must be continued in the manufacturing and use phase.

Each medical device manufacturer must have an effective program for: identifying failure patterns or trends and analyzing quality problems; taking appropriate corrective action to prevent recurrence of these problems; and timely internal reporting of problems discovered either in-house or in the field. Specific instructions should be established to provide direction about when and how problems are to be investigated, analyzed, and corrected, and to establish responsibility for assuring initiation and completion of these tasks.

When problem investigation and analysis indicate a potential problem in the design, appropriate design improvements must be made to prevent recurrence of the problem. Any design changes must undergo sufficient testing and preproduction evaluation to assure that the revised design is

safe and effective. This testing should include testing under actual or simulated use conditions and clinical testing as appropriate to the change.

A special effort should be made to assure that failure data obtained from complaint and service records that may relate to design problems are made available and reviewed by those responsible for design.

REFERENCES

MILITARY STANDARDS

1. MIL-STD-1629 Procedures for Performing Failure Mode, Effects and Criticality Analysis
2. MIL-STD-785B Reliability Program for Systems and Equipment Development and Production
3. MIL-STD-109B Quality Assurance Terms and Definitions
4. MIL-STD-217B Reliability Prediction of Electronic Equipment
5. MIL-STD-472 Maintainability Predictions
6. MIL-STD-1521 Technical Reviews and Audits for Systems, Equipments, and Computer Programs
7. MIL-STD-781C Reliability Design Qualification and Production Acceptance Tests: Exponential Distribution
8. MIL-STD-483 Configuration Management

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

1. NASA SP-6502 Elements of Design Review for Space Systems
2. NASA SP-6504 Failure Reporting and Management Techniques in the Surveyor Program
3. NHB 5300.4(A) Reliability Program Provisions for Aeronautical and Space System Contractors
4. N68-1 01 20 Parts and Materials Application Review for Space Systems
5. N68-20357 An Introduction to the Assurance of Human Performance in Space Systems

VOLUNTARY STANDARDS

1. ANSl/ASQC Z-1.15-1979 Generic Guidelines for Quality Systems

2. ASQC C1 -1 968 — Specification of General Requirements for a Quality Program
3. ANSI/IEEE STD 730-1984 — IEEE Standard for Software Quality Assurance Plans
4. ANSI/IEEE STD 830-1981 — Guide to Software Requirements Specifications
5. IEC 1160 — IEC Guide on Formal Design Review

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2. Juran, J.M., "Quality Control Handbook." 3rd edition, McGraw-Hill, N.Y. (1974).
3. Lloyd, David K. & Lipow, Myron, "Reliability: Management, Methods, and Mathematics." Prentice-Hall, N.J. (1964).

Others

1. RDH-376 "Reliability Design Handbook." Reliability Analysis Center, Rome Air Development Center, Griffiss Air Force Base, N.Y. (1976).
2. NBS* Special Publication 500-98, "Planning for Software Validation, Verification, and Testing." (November 1982).
3. NBS* Special Publication 500-75, "Validation, Verification, and Testing of Computer Software." (February 1981).
4. NBS* Special Publication 500-56, "Validation, Verification, and Testing for the Individual Programmer." (February 1980).

NBS Federal Information Processing Standards Publications (FIPS PUBS)

1. FIPS PUB 38, "Guidelines for Documentation of Computer Programs and Automated Data Systems." (February 1976).
2. FIPS PUB 64, "Guidelines for Documentation of Computer Programs, and Automated Data Systems for the Initiation Phase." (August 1979).
3. FIPS PUB 101, "Guidelines for Lifecycle Validation, Verification, and Testing of Computer Software." (June 1983).

* NBS (National Bureau of Standards) is now the National Institute of Science and Technology.